INTRODUCTION

Polycystic ovary syndrome (PCOS), is a complex neuroendocrine-metabolic disorder, which is associated with insulin resistance and a high prevalence of obesity, ***(Dunaif 1995).***

PCOS appears to be associated with an increased risk of metabolic aberrations, including insulin resistance and hyperinsulinism, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial carcinoma ***(Dunaif et al 1995, Ehraman 1997, Legro et al 1999).***

Insulin resistance in PCOS appears to be independent of, but is amplified by obesity, ***(Holte et al 1994 , Morales et al 1996).***

Recently, several laboratories have investigated the cellular mechanism(s) underlying insulin resistance in PCOS employing a classical insulin target tissue, isolated adipocytes. The most striking common finding in these studies was a large reduction in insulin sensitivity for glucose transport stimulation in the face of normal insulin binding. Thus, insulin resistance in PCOS represents postbinding defects in signal transduction, ***(Marsden et al 1994).***

For research purposes, many investigators define PCOS using the recommendations of a conference sponsored by the National Institutes of Health (NIH)/National Institute of Child Health and Human Development in April 1990 , The conference concluded that PCOS should be defined by the following (in order of importance):

1) Hyperandrogenism and/or hyperandrogenemia,

2) Ovulatory dysfunction, and

3) Exclusion of related disorders such as hyperprolactinemia, thyroid disorders, and non-classical adrenal hyperplasia ***(***(***Vollenhoven et al 2000***).

Efforts have been made to further characterize the insulin resistance in adipocytes from obese PCOS and weight-matched normal cycling (NC) women. The study was done for observation of that experimentally induced depletion of cellular adenosine in rat adipocytes resulted in an impaired insulin sensitivity of glucose transport stimulation with normal binding, a condition that resembles the behavior of adipocytes in PCOS, ***(Ciaraldi et al 1988).***

There was a wide variety of views among the assembled experts regarding the clinical and endocrinologic features that characterize polycystic ovary syndrome. Many practical and useful clinical definition of polycystic ovary syndrome has emerged in the United States. However according to NIHC, women are defined to have polycystic ovary syndrome if they have chronic anovulation and evidence of androgen excess for which there is no other cause. This is often referred to as the "NIH Conference" definition, despite the variability in the responses ***(National Institute of Health).***

Definition Of PCOS

Rotterda ESHRE/ASRM:

Since the 1990 National Institutes of Health-sponsored conference on polycystic ovary syndrome (PCOS), it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of

ovarian dysfunction than those defined by the original diagnostic criteria. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology. PCOS remains a syndrome, and as such no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. Its clinical manifestations may include menstrual irregularities, signs of androgen excess, and obesity. Insulin resistance and elevated serum LH levels are also common features in PCOS. PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events, (**Revised 2003 consensus on diagnostic criteria and long-term health risks related to PCOS).**

Accorrding to NIH/NICHHD:

The classic symptoms of amenorrhea, infertility, hirsutism and obesity do not all need to be present to suspect a diagnosis of polycystic ovary syndrome . Although considerable controversy remains concerning the definition of PCOS. Several investigators have used a working definition from a 1990 National Institutes of Health/National Institute of Child Health and Human Development ***(NIH/NICHHD)*** Conference ***(Zawadzki and Dunaif, 1992).***

To fit this definition, a patient must have ovulatory dysfunction and evidence of hyperandrogenism, clinically or by laboratory means, but no other causes of hyperandrogenism. Laboratory and radiographic studies are important in excluding other causes of these symptoms ***(Frank 1995, and Taylor 1998).***

Menstrual symptoms, often with perimenarcheal onset, are the most common finding among women with PCOS **(*Franks 1995).***

Recently, PCOS is characterized by taking values for the diagnostic criteria of the syndrome increased follicle number and ovarian volume, elevated serum LH and testosterone above the 95^{th} percentile a control population **(*Van Santbrink and Coworkers 1997).***

Overall, the clinical presentation is critical to the diagnosis of PCOS, which has been defined as ovulatory dysfunction and hyperandrogenism in the absence of other causes. Most ovulatory dysfunction can be suspected based on history, with targeted hormonal testing to corroborate it. Physical findings suggestive of hyperandrogenism provide the next critical step in a diagnosis of PCOS. An assessment of obesity and fat distribution should be a part of the physical examination because metabolic features of the disorder are important not only in diagnosis but also in therapy ***(Zawadzki and Dunaif 1992).***

However, since gonadotropin concentrations vary over the menstrual cycle and are released in a pulsatile fashion into the circulation, a single measurement of luteinizing hormone and follicle-stimulating hormone provides little diagnostic sensitivity. Thus, in routine clinical practice, abnormal gonadotropin levels (an elevated level of luteinizing hormone or an elevated ratio of luteinizing hormone to follicle-stimulating hormone) need to be documented to diagnose the polycystic ovary syndrome. Chronic anovulation most often manifests as oligomenorrhea (fewer than nine menses per year) or amenorrhea. Anovulatory cycles may lead to dysfunctional uterine bleeding and decreased fertility. Cutaneous manifestations of hyperandrogenemia in the polycystic ovary syndrome include hirsutism, acne, and male-pattern

hair loss (androgenic alopecia), whereas acanthosis nigricans is a cutaneous marker of hyperinsulinemia**.** A substantial proportion of women with the polycystic ovary syndrome are overweight; many are obese, some extremely obese. Although obesity itself is not considered the inciting event in the development of the syndrome, excess adiposity can exacerbate associated reproductive and metabolic derangements, ***(Ehrmann et al 1999).***

Polycystic ovary syndrome usually begin around menarche, ***(Franks et al 2002***), but onset after puberty may also occur as a result of environmental modifiers such as weight gain. Premature pubarche, the result of early secretion of adrenal steroids, may be a harbinger of the syndrome, ***(Ibanez et al 2001).***

Prevalence of PCOS

There is little idea about the true incidence of PCOS, as most of the cases depend on suspicion and on diagnostic criteria of individual clinician ***(Farquhar et al., 1994).***

The syndrome is seen in the second and third decades of life. The great majority of the PCOS patients were first seen between the age of 20 and 30 years ***(Raj et al., 1997).***

Most studies of the prevalence of polycystic ovary syndrome yield unreliable results because of the selection bias that occurs when a referral center for polycystic ovary syndrome reports on its experience. The best prevalence study, reported in 1998, was based on an unselected sample of white and African-American women between the ages of 18 and 45 years who were presented for a physical employment in University in Alabama, ***(Knochenhauer et al 1998).***

Of 277 women who consented to a history, physical examination, and hormonal evaluation, the overall prevalence of polycystic ovary syndrome by using the above definition was 4–4.7% for white women and 3.4% for African American women. This implies that approximately 3 million reproductive-aged women in the United States have polycystic ovary syndrome **, *(Knochenhauer et al 1998).***

Clinical Importance of PCOS

In clinical gynecologic practice, women with polycystic ovarian syndrome are seen primarily for menstrual irregularity, androgen excess, and infertility. Treatment is largely directed at the immediate presenting complaint. During the past decade, women with chronic anovulation and hyperandrogenism have been observed to have an increased prevalence of diabetes and increased risk factors for coronary heart disease (CHD). Specifically, many women with polycystic ovary syndrome are similar to those with metabolic cardiovascular syndrome (ie, Syndrome X), a CHD-associated clustering within the same individual of hyperinsulinemia, glucose intolerance, dyslipidemia, and hypertension. In addition, the chronic anovulation of polycystic ovary syndrome implies unopposed estrogen and, therefore, an increased risk of endometrial cancer. These factors have led to a different clinical perspective about polycystic ovary syndrome—one that recognizes the importance of addressing the immediate issues of irregular bleeding, hirsutism, and infertility, but also emphasizes the long-term goals of preventing diabetes, heart disease, and cancer.

AETIOLOGY OF PCOS

The aetiology of polycystic ovarian syndrome is uncertain until now. There is some evidence of autosomal transmission still related to strong familial clustering. Potentially, a gene or series of genes renders the ovaries susceptible to insulin stimulation of androgen secretion while blocking follicular maturation, ***(Nestler 1997).***

This genetic predisposition may be expressed as premature balding in men, ***(Carey et al 1993).*** The onset may occur in late childhood since many of the metabolic and endocrine features of the disorder mimic puberty, ***(Nobels et al 1992),*** Insulin resistance increases dramatically at the onset of puberty and then declines in early adulthood. Associated with this are increases in the pulse amplitude of luteinising hormone, increasing androgen concentrations, and irregular menses. Multiple, small ovarian cysts are seen on ultrasound examination and are a common and normal feature of puberty. It is therefore possible that women genetically predisposed to polycystic ovarian syndrome fail to resume normal insulin sensitivity and continue to express metabolic and endocrine features usually confined to puberty ***(Nobels et al 1992).***

I- Hereditary Factors in PCOS:

Polycystic ovary syndrome may be an X-linked dominant inherited disorder. The increased menstrual abnormalities, and hair growth abnormalities (bund in female, relatives of patients with PCOS, and also embryonic-like cells in the ovaries of some patients support the concept of a genetic basis of PCOS. This encountered 4 individuals who possess PCOS and some features of the phenotypic finding seen in Turner's syndrome, (***Vaitukaitis 1988)***.

II- Endocrinological Factors in PCOS:

a) Hypothalamic-Pituitary Abnormality:

It has been suggested that a primary hypothalamic-pituitary abnormality might underlie the acyclic increased pulsatile LH and relatively low FSH in the PCOS. However, since the hypothalamic-pituitary can respond normally to estrogen feedback, and since ovulation can be induced with clomiphene citrates, or by wedge resection of the ovaries, a primary abnormality seems unlikely. It is probable that the increased LH release is due to increased pituitary sensitivity to LH releasing hormone caused by increased unbound androgen and estrogen levels. Increased LH release in response to LHRH has been demonstrated in several studies, whereas FSH release is similar to that in the early follicular phase. Another, unsubstantiated theory is that increased inhibin production by PCO might affect pituitary FSH release ***(Yen, 1980).***

b) Ovarian Endocrine Abnormality:

Erickson and Colleagues (1979), showed that ability to aromatize is related to follicle size. Granulosa cells from small follicles (4-6 mm diameter) from both normal and polycystic ovaries were unable to aromatize whereas cells from larger follicles (8-15 mm) can aromatize added androstenedione. Addition of FSH and androstenedione to cultured granulosa cells from both polycystic and normal ovaries resulted in a marked increase in estrogen production not seen following the addition of LH and androstenedione. Similarly, parental administration of FSH to patients with polycystic ovaries results in a rapid increase in circulating estrogen levels. higher levels of androstenedione than oestradiol in

follicles with no FSH and higher levels of oestradiol than androstenedione in follicles containing FSH, throughout the menstrual cycle. It is thought that theca cells, under the stimulation of LH, provide androstenedione substrate for estrogen synthesis by granulosa cells, (***Erickson and Colleagues 1979)***

C. Adrenal Abnormality:

Approximately 4% of women of reproductive age present with hyperandrogenism and oligo-ovulation, signs and symptoms consistent with the polycystic ovary syndrome, ***(Knochenhaver et al., 1998)***.

Of PCOS women, 25% to 60% have been reported to have adrenal androgen excess, including elevations in the levels of dehydroepiandrosterone sulfate (DHEA-S) or 11β-hydroxyandrost-enedione (11-OHA4), 90% of which are produced by the adrenal cortex **(*Moran et al., 1999).***

The adrenal excess in PCOS is caused by multiple and complex factors. There is a pathophysiologic interconnection between the ovary and the adrenal in PCOS patients. For example, ovarian products can promote adrenal androgen production ***(Fruzzetti et al., 1995),*** and, conversely, adrenal androgens can serve as precursors of ovarian steroidogenesis ***(Hanning et al., 1991).***

Furthermore, other factors often present in PCOS patients, including hyperinsulinemia and insulin resistance, and can affect the secretion of adrenal androgen ***(Nestler et al., 1989).***

Although some investigators have proposed the use of 11-OHA4 as an alternative marker of adrenal androgen excess the authors have found

that the radioimmunoassay for this steroid is difficult to perform and standardize, ***(Carina et al., 1995)***.

Serum levels of DHHAS and 11-OHA4 have been reported to be elevated in 25% to 60% of patients with PCOS ***(Moran et al., 1999),*** setting the upper normal limit by studying a group of healthy controls. Nonetheless, adrenal androgens begin to decline after age 30 years ***(Ruutiainen et al., 1988).***

Peak adrenal androgen concentrations occur around age 20 years, decreasing in a linear fashion thereafter; therefore, many young patients with PCOS will be diagnosed as having adrenal androgen excess if age-matched controls are not used, in a retrospective study of 145 hyperandrogenic patients with hirsutism with or without oligo-ovulation, the authors noted that patients with high DHEA-S levels were younger, thinner, and more hirsute when compared with hyperandrogenic women with normal or lower DHEA-S levels. Furthermore, an age-related decline in DHEA-S levels was observed with age in hyperandrogenic women and healthy controls. These findings suggested that the diagnosis of adrenal androgen excess, with or without PCOS, requires the use of age-adjusted normal values ***(Moran et al., 1999).***

III- Metabolic Factors of PCOS:

a) Obesity and PCOS:

The prevalence of obesity in PCOS populations, although high, is variable among large series ***(Legro, 2000).***

In an English population of 1741 women diagnosed with PCOS based on ultrasound examination of the ovaries, 38.4% were overweight as defined by a BMI of 26 or greater ***(Balen et al., 1995).***

Other studies have found that the prevalence of obesity in PCOS patients is much higher. Among 280 women in Pennsylvania diagnosed with PCOS based on clinical criteria (chronic anovulation plus androgen excess), the majority (87.5%) had a BMI of 26 or greater. In a report from New York City, 60% of PCOS patients defined by elevated androgens and anovulation were classified as obese (>20% over ideal body weight). The prevalence of obesity in PCOS in a population may be influenced by the diagnostic criteria used to define the syndrome, as well as geographic and environment factors ***(Dunaif et al., 1987).***

The reason for the high prevalence of obesity in women with PCOS is unknown. Moreover, it is unclear that obesity is the primary insult among women with PCOS because lean women also manifest the disorder. Obesity is not a homogenous condition. Body fat distributed in an android pattern, that is, central obesity, is defined as excess fat on the trunk, either subcutaneously or in the abdominal viscera. In contrast, gynecoid obesity presents a relative increase in fat accumulation in the gluteofemoral or hip area ***(Lefbvre et al., 1997).***

The type of obesity can be determined by calculating the waist-to-hip ratio (WHR), the most widely used anthropomorphic method that distinguishes between abdominal and peripheral body fat distribution. In general, a WHR of greater than 0.8 is consistent with central or android obesity. In a study of body fat distribution in women with PCOS, 63% were found to have a WHR greater than 0.3 ***(Pasquali et al., 1989).***

Other investigators have shown that the site of fat accumulation in women is an important predictor of susceptibility to metabolic changes. For example, central obesity is associated with decreased glucose tolerance and hyperinsulinemia in premenopausal women after controlling for BMI. Women with PCOS identified with central obesity had higher androgen, glucose, and lipid levels as well as an increase in diastolic blood pressure when compared with women with peripheral fat distribution after controlling for age and BMI. These adverse changes in metabolic parameters and cardiovascular risk profile seen with increasing WHR may disproportionately affect obese women with PCOS, who have an increased prevalence of central obesity ***(Kissebah et al., 1992).***

b) Insulin Sensetivity and PCOS:

Dunaif et al (1987), described a significant impairment of glucose metabolism in obese patients with PCOS when compared with ovulatory women matched by age and weight. Twenty percent of the obese PCOS patients had impaired glucose tolerance or frank non-insulin-dependent diabetes mellitus (NIDDM), however, similar levels of glucose intolerance were not seen in the non-obese women when compared with age and-weight-matched controls despite the finding of insulin resistance in the non-obese PCOS patients, ***(Dunaif et al; 1987)***.

Subsequent studies by ***Dunaif 87***, have found glucose intolerance in as many as 40% of obese PCOS women. The prevalence rates of 20% to 40% for impaired glucose tolerance in this population are substantially higher than the 7.8% rate reported in population-based studies on the

incidence of glucose intolerance in women of similar age ***(Dunaif et al; 1987)***.

Non-obese PCOS patients were found to have a higher rate of impaired glucose tolerance (10.3%) and N1DDM (1.5%) than age-matched controls in a subsequent study by Legro (1999), and this rate was two to threefold higher in an obese PCOS patient population. These findings suggest that obesity and PCOS confer increased and additive risks of impaired glucose tolerance and NIDDM. These metabolic abnormalities occur at an early age, patients in these studies were aged 14 to 44 years, ***(Legro et al., 1999),***.

Obesity, body fat location (assessed by increased WHR), and muscle mass have important independent effects on insulin sensitivity ***(Dunaif, 1999).***

Basal hepatic glucose production and the half-maximal dose of insulin for suppression of hepatic glucose production, as measured by the euglycemic glucose clamp technique, are significantly increased in obese women with PCOS. This synergistic effect is an important pathway in the pathogenesis of glucose intolerance in PCOS. The genetic defects in insulin action seen in PCOS seem to combine with obesity-related insulin resistance to produce impaired glucose tolerance and N1DDM **(*Dunaif, 1989).***

Pathophysiology of

Polycystic Ovary Syndrome

Polycystic ovarian disease may stem from higher centers, hypothalmous, pituitary, adrenal or from the ovaries. It may originate from excess of fat tissue usually combined with hyperinsulinemia or may be the net increase in active growth factors. Each of the above disturbances appears early in life much before the clinical signs of the disease are evident ***(Insler and Lunenfeld, 1991).***

No single etiologic factor fully accounts for the spectrum of abnormalities in the polycystic ovary syndrome. In response to stimulation by luteinizing hormone, the ovarian theca cell synthesizes androgens . Androgen biosynthesis is mediated by cytochrome P-450c17, an enzyme with 17α-hydroxylase and 17,20-lyase activities, both of which are required to form androstenedione. The androgenic steroid is then converted by 17β-hydroxysteroid dehydrogenase (17β-HSD) to form testosterone or is aromatized by the aromatase enzyme (cytochrome P-450arom) to form estrone. Studies performed both in vivo and in vitro (in cultured theca cells) consistently suggest that ovarian theca cells in affected women are more efficient at converting androgenic precursors to testosterone than are normal theca cells, ***(Nelson & Qin et al 2001).***

The Hypothalamic–Pituitary–Ovarian Axis and the Role of Insulin: Increased ovarian androgen biosynthesis in the polycystic ovary syndrome results from abnormalities at all levels of the hypothalamic–pituitary–ovarian axis. The increased frequency of luteinizing hormone (LH) pulses in the polycystic ovary syndrome appears to result from an increased frequency of hypothalamic

gonadotropin-releasing hormone (GnRH) pulses. The latter can result from an intrinsic abnormality in the hypothalamic GnRH pulse generator, favoring the production of luteinizing hormone over follicle-stimulating hormone (FSH) in patients with the polycystic ovary syndrome, in whom the administration of progesterone can restrain the rapid pulse frequency. By whatever mechanism, the relative increase in pituitary secretion of luteinizing hormone leads to an increase in androgen production by ovarian theca cells. Increased efficiency in the conversion of androgenic precursors in theca cells leads to enhanced production of androstenedione, which is then converted by 17β-hydroxysteroid dehydrogenase (17β) to form testosterone or aromatized by the aromatase enzyme to form estrone. Within the granulosa cell, estrone is then converted into estradiol by 17β. Numerous autocrine, paracrine, and endocrine factors modulate the effects of both luteinizing hormone and insulin on the androgen production of theca cells; insulin acts synergistically with luteinizing hormone to enhance androgen production. Insulin also inhibits hepatic synthesis of sex hormone–binding globulin, the key circulating protein that binds to testosterone and thus increases the proportion of testosterone that circulates in the unbound, biologically available, or "free," state. Testosterone inhibits and estrogen stimulates hepatic synthesis of sex hormone–binding globulin. The abbreviation SCC denotes side-chain cleavage enzyme, (STAR), steroidogenic acute regulatory protein, and 3β-HSD 3β-hydroxysteroid dehydrogenase. Solid arrows denote a higher degree of stimulation than dashed arrows ***(Nelson & Qin et al 2001).***

Whereas luteinizing hormone regulates the androgenic synthesis of theca cells, follicle-stimulating hormone is responsible for regulating the aromatase activity of granulosa cells, thereby determining how much

estrogen is synthesized from androgenic precursors. When the concentration of luteinizing hormone increases relative to that of follicle-stimulating hormone, the ovaries preferentially synthesize androgen, ***(Nelson & Qin et al 2001).***

The frequency of the stimulus of hypothalamic gonadotropin-releasing hormone (GnRH) determines, in part, the relative proportion of luteinizing hormone and follicle-stimulating hormone synthesized within the gonadotrope. Increased pulse frequency of hypothalamic GnRH favors transcription of the β-subunit of luteinizing hormone over the β-subunit of follicle-stimulating hormone; conversely, decreased pulse frequency of GnRH favors transcription of the β-subunit of follicle-stimulating hormone, which decreases the ratio of luteinizing hormone to follicle-stimulating hormone, ***(Haisenleder et al 1991).***

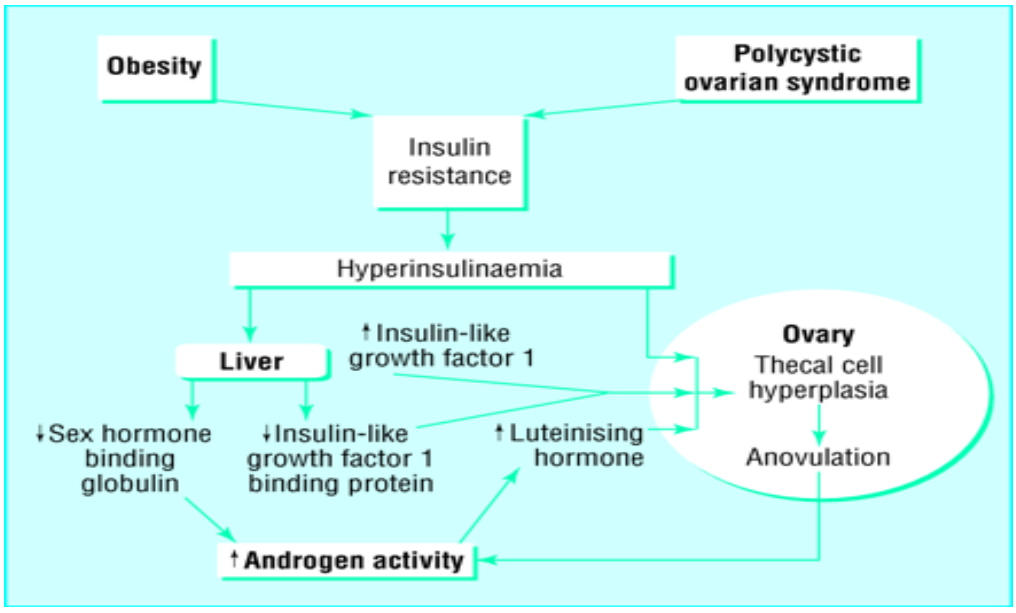


Fig. 1. Probable mechanisms whereby defects in insulin metabolism promote increased androgen activity at the level of the ovary *(Cataldo 1997).*

Because women with the polycystic ovary syndrome appear to have an increased luteinizing hormone pulse frequency ***,(Waldstreicher***

et al; 1991), it has been inferred that the pulse frequency of GnRH must be accelerated in the syndrome. It is not clear whether this accelerated pulse frequency is due to an intrinsic abnormality in the GnRH pulse generator or is caused by the relatively low levels of progesterone resulting from infrequent ovulatory events. Since progestins slow the GnRH pulse generator, low circulating progestin levels in women with the polycystic ovary syndrome may lead to an acceleration in the pulsatility of GnRH, increased levels of luteinizing hormone, and overproduction of ovarian androgen, ***(Eagleson et al; 1988).***

Good evidence supports the hypothesis that decreased peripheral insulin sensitivity and consequent hyperinsulinaemia are pivotal in the pathogenesis of polycystic ovarian syndrome, ***(Dunaif 1997).***

Peripheral insulin resistance is most evident in overweight patients: obesity and polycystic ovarian syndrome each seem to have a separate and synergistic relation with insulin resistance ***(Dunaif 1997).***

The exact mechanism(s) for insulin resistance is uncertain, but a post-receptor defect in adipose tissue has been identified, ***(Dunaif 1997).***

Despite insulin resistance in adipose and skeletal muscle, the ovary remains relatively sensitive to insulin, and both insulin and insulin-like growth factor 1 have stimulatory effects on thecal androgen production, ***(Bergh et et al 1993).***

In fact, some lean women with polycystic ovarian syndrome, who may not have insulin resistance and therefore hyperinsulinaemia, may show enhanced ovarian sensitivity to insulin. the relative excess of insulin or enhanced ovarian sensitivity to insulin, in combination with an elevated luteinising hormone concentration, brings about thecal

hyperplasia, increased androgen secretion, arrest of follicular development *(Figure 1)*, and therefore anovulation along with menstrual disturbance, ***(Cataldo 1997).***

Insulin also acts on the liver to inhibit the production of sex hormone binding globulin and insulin-like growth factor 1 binding protein. A reduction in sex hormone binding globulin leads to an increase in the biologically available free testosterone. Thus, insulin resistance not only increases secretion of ovarian androgens but also promotes an increase in the proportion of free (active) hormone. Similarly, inhibition of production of insulin-like growth factor 1 binding protein results in an increased concentration of circulating free insulin-like growth factor 1, further enhancing ovarian androgen production, ***(Cataldo 1997).***

Pathophysiology & Endocrinal

Abnormalities in PCOS

Hormonal Changes in PCOS:

1.Gonadotropins:

Out of 78 patients with PCOS, 40 patients had normal LH level as those of normal women, 35 patients had normal LH/FSH ratio. This was attributed to the variability of LH level by time. One explanation for a normal LH levels is that it may not be representative of temporal pattern of LH secretion and for this reason it has been suggested that the mean levels of three samples should be considered ***(Futtlewiet, 1984).***

Nevertheless, there remains a number of women with PCOS who have persistently normal concentrations of LH and this implies that a raised LH/FSH ratio is not an essential feature of anovulatory cycles in PCOS ***(Franks et al., 1985).***

Both 8- hour mean LH and LH-pulse amplitude are significantly increased in PCOS women but that LH pulse frequency remains unaltered, (***Smith and Franks 1993)***.

Smith and Frank 1993,studied 9 patients with PCOS and 12 normal women and observed that there is no difference in the pluse frequency occurred between the two groups. The different conclusions of these separate studies may result from different study populations, alternatively, any differences in pulse may be too small to detect***, (Smith and Frank 1993).***

It is still unclear whether the hypersecretion of LH in PCOS result from a primary hypothalamic disturbance or is secondary to ovarian dysfunction, ***White et al (1995),*** studied 24-hours LH pulse secretion in three groups of 10 women: anovulatory women with polycystic ovaries, ovulatory women with poly cystic ovaries, and control subjects. They found that 24-hours mean LH values in both PCOS groups were significantly higher than in the controls. But noted a sleep-related slowing of LH pulse only in the ovuiatory women. These data indicate that despite having elevated 24 hour mean levels of LH, ovulatory women with polycystic ovaries have evidence of a normal hypothalamic regulation of LH they suggested that, in PCOS, there is no primary hypothalamic disturbance of LH secretion and that the increase in pulse frequency observed in anovulatory PCOS subjects occurs secondary to the

endocrine environment associated with chronic anovulation, (***White et al, 1995)***.

2. Androgen:

Hyperandrogenism is the primary dysfunctional feature of PCOS. The excess androgen production originates from the ovaries and often also from the adrenal cortex, ***(Lachelin 1984).***

Vermeuler 1979, *have* shown an increase in unbound testosterone concentration, in the PCOS patients, the mean value for unbound testosterone, in 15 PCOS patients was about times the normal mean value, with only three patients failling within the high normal range. This difference was highly significant,(***Vermeuler et al. 1979)***.

Takai et al., (1991) re-evaluated the concept of PCOS in view of androgenic function. According to their study, it was possible to divide PCOS patients into three types:

1. Patients with neither hirsutism nor elevation of serum androstenedione and/or testosterone were defined as type I PCOS.
2. Patients without hirsutism but with elevated androstenedione and/ortestosterone were referred to as type II PCOS.
3. Patients with both hirsutism and elevation of androstenedione and/ortestosterone were defined as type III PCOS.

Concentrations of androstenedione appeard gradually increasing in types I, II, III.

Source of androgen excess:

Although evidence supported a combined source of androgen excess, only 50% of PCOS patients have elevated levels of adrenal androgen. However an exaggerated adrenal DHEA and ovarian 17-hydroxy progesterone response to exogenous ACTH stimulation is common in PCOS patients, this was explained by Rosenfield who assumed hyperfunction of P-450 C_{17} the androgen forming enzyme to co exist in both the ovary and the adrenal in PCOS patients, ***(Rosenfield and Associates 1990).***

In anovulatory women with polycystic ovaries, there is an approximate 50% reduction of circulating levels of SHBG, as a response to the increased testosterone. In patients with hyper insulinemia the direct effect of insulin on the liver leads to decrease SHBG production, ***(Speroff et al, 1994(b)).***

The most important determinant of SHBG concentration is the body mass index (BMI), i.e weight (kg) / height $(m)^2$ SHBG concentrations were significantly lower in the obese patients and free testosterone concentration significantly higher, so the higher prevalence of hirsutism was observed in the obese women, (***Smith and Franks 1993).***

Weight reduction is associated with marked increase in SHBG, fall in free testosterone and fall in both fasting insulin level , and also decrease in the level of post-prandial blood sugar response to a 75 gm oral glucose test, (***Kiddy et al., 1992).***

This supports the theory that resumption of ovulatory cycles following significant weight loss could be related to an increased insulin

sensitivity in the previously insulin resistant ovary, which in turn, affects the ovarian response to gonadotropins, (***Smith and Franks 1993).***

The maximum increase in testosterone, androstenedione, 17 hydroxyprogesteron and DHEA-S in response to ACTH was in the high DHEA-S group of PCOS women, (***Fruzzelti et al., 1995)***.

Serum testosterone levels are raised in all groups of women with ultrasonographic evidence of PCOS although the values arc highest in those who arc anovulatory and hirsute, (***Frank, 1991).***

Women with PCOS may have testosterone level up to 10ng/dl (reference range 0.5 - 2.6 ng/dl)**,** but hirsute women may manifest testosterone level 20-80 ng/dl, ***(Hamilton-Fairley and Pearce 1993***).

There is no direct correlation between the level of hirsutism and the total concentration of testosterone because hirsutism is caused by the action of testosterone metabolite dihydrotest-osterone, which in turn is related to concentration of SHBG, ***(Hershlag et Peterson 1996).***

Normal free serum testosterone is (0.3 - 1.9/ ng/ml), (***Hershlag and Peterson, 1996).***

LH and FSH secretion in response to luteinizing hormone releasing horme (LHRH) stimulation were lowered in parallel manner from type I through type II PCOS. This unexpected observation was explained by the high androstenedione and testosterone levels that seemed to have a suppressive action on both LH and FSH. They also excluded the oetrogen effect on the pituitary (as its level was more or less similar in the three types), ***(Takai et al. 1991)***.

Elevation of virtually all androgenic hormones and their precursors have been found in patients with PCOS. These include, testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulphate (DHEAS). In addition 17 α hydroxy progesterone concentrations are elevated, in patients with PCOS. ***(Lachelin et al., 1979).***

3. Estrogen:

A detailed comparison of nine patients with PCOS and six ovulatory women in the early follicular phase. They found that the mean plasma estrone concentrations were greater in PCOS patients (490 p mol/L) than in the control group (295 p mol/L). The results for oestradiol were closer (275 p mol/L versus 210 p mol/L) but still significantly different, (***Baird et al.1977)***.

Although estradiol secretion by the ovaries in PCOS is frequently reduced ***Yen, 1980***, the maintenance of follicular phase levels of estradiol represents the sum of these derived from extra glandular conversion of testosterone to estradiol and inter conversion of estrone to estradiol, ***(Longcope and Williams, 1974)***.

It has been estimated that about 0.4 percent of testosterone entering the circulation is converted to estradiol, ***(Judd et al., 1982)***.

At the same time, the free estradiol levels are increased because of the significant decrease in SHBG that occurs in PCOS **,** ***(Yen, 1980)***.

The source of this excess estrogen in the PCOS patients has been defined unequivocally. It may be due to direct ovarian secretion or due to peripheral conversion of androstendion. Similarly, some of estradiol might be a rise through the peripheral conversion of testosterone **(*Edman and Mc Donald, 1988)***.

Aromatization of androgen to estrogens has been demonstrated in several tissue sites where aromataze enzyme is present such as Muscle and adipose tissue which are the major sites of aromatization, liver, skin fibroblasts and their follicles, brain especially the hypothalamus, and Bone marrow, (***Yen, 1991)***,.

Estrogens in pathophysiology of PCOS:

Normal levels of total estradiol with increased levels of unbound E_2 was observed in women with PCOS. These high unbound E_2 levels resulted from the lowered SHBG and the sequentially decreased binding capacity (SHBG- BC), ***(Lobo et al. 1981)***.

Elevated unbound E_2 was found to act on the hypothalamic pituitary level increasing, LH:FSH ratio in women with PCOS ***(Lobo et al., 1981).***

The estrogenic role in PCOS was detected by administration of estrone benzoate in a group of PCOS women, it was found that FSH was reduced while LH release was unaltered, ***(Chang et al 1982)***.

4- Prolactin:

In a series of 394 women, reviewed by, (***Futterweit, 1984)***, raised serum prolactin concentrations were found in 27 percent, of patients with

PCOS. In Futterweit's own group of patients (16-18 percent) had hyperprolactinemia.

Frank et al.,(1985) have found a rather lower figure, as 6 out of 137 cases (4.5 percent) had hyperprolactinemia.

The association of elevated prolactin with PCOS may be due to one of three possible mechanisms: Abnormal central neurotransmission, Increased activity of the lactotrophs, or as a distinct clinical entity, ***(Cumming et al., 1981).***

It is possible that the unopposed action of estrogen on the pituitary causes the raised prolactin ***(McKenna, 1988).***

The precise cause of elevated serum prolactin in some women with PCOS is unclear, ***(Gilling et al., 1993)***.

The basal prolactin levels and the prolactin response to sulpiride (dopaminergic receptor blocking agent) were increased in women with PCOS. In women with PCOS, medical ovariectomy induced by GnRHa administration reversed to normal both basal and sulpiride-stimulated prolactin levels, they concluded that in women with PCOS, the abnormal regulation of prolactin and presumably of hypothalamic neurotransmitters controlling prolactin secretion is not a primary alteration but it is likely dependent on abnormal ovarian functionality, ***(Paoletti et al. 1995),***.

It was found that a mild increase in circulating prolactin (30-80ng/ml) may cause an inadequate corpus luteum or inhibit ovulation, where a more severe hyperprolactinemia (100 ng/ml) usually produce amenorrhea and hyper estrogenic stale ***(Speroff et al., 1994a).***

5- Endogenous opioids in PCOS:

Endogenous opioids may affect hypothalamic GnRH, it has been demonstrated that β-endorphins decrease hypothalamic and increase striatal dopamine turnover. Encephalin also has been sown to block dopamine induced GnRH release from the rat mediobasal hypothalamus ***(Yen, 1980).***

Based on such finding ***(Elitalu et al., 1983)*** suggested an interaction among dopamine opioid peptides and GnRH secretion or a functional dissociation of opioid neuronal activity in PCOS. Peripheral levels of β-endorphin have also been found to be significantly high in patients with PCOS ***(Aleem and Mclntosh, 1984).*** Furthermore, patients who weighted more, demonstrated even higher levels both β-endorphin and adrinocorticotrophic hormone (ACTH) are derived from the same precursor and it is known that β-endorphin is increased in conditions with increased ACTH production ***(Hollt et al., 1979).***

However, ACTH levels and cortisol production are normal in PCOS ***(Chang et al., 1983).***

Neurologic and Psychological Considerations in PCOS

Neurologic factors may modulate GnRH and may contribute to the pathophysiology of PCOS. Impulses discharged in the amygdala, which is extremely connected to the hypothalamic pre-optic and ventromedial nuclei, may modulate dopamine as well as GnRH secretion. The

ventromedial nucleus is described to contain the satiety center explaining the occurrence of obesity in PCOS ***(Herzog et al., 1986).***

Psychological stress may be prevalent in young women with PCOS. Moreover, psychological stress may be associated with elevated level of β-endorphins and other neurotransmitters such as norepinephrin and serotonin. because (here may be an association between β-endorphins, norepinephrine, serotonin and the LH-androgen levels in women with PCOS, they hypothesed that psychological stress may be implicated in the pathophysiology of PCOS, (***Lobo et al., 1983)***.

Lipid Metabolism in Normal Women

Lipoproteins are assemblies of lipids and specialized proteins "apoproteins" whose primary function in lipid metabolism is the transport of lipids to or from sites of synthesis or catabolism. The lipoprotein particles arc spherical macromolecular entity with a non-polar hydrophobic core containing lipids, triglyceride (TGs) or cholesterol esters. A unipolar layer shell of phospholipids in which specific apoproteins are embedded surrounds it. The polar nature of the lipoprotein shell helps to solubilise the particle in an aqueous medium and assure relative stability while it is circulating ***(Wild, 1991)***.

The major apoproteins are called E, C, B48, which is a low molecular weight form of the characteristic exogenous system that transport exogenous ingested lipids and B_{100} which is a high molecular weight form of the endogenous system Mini transport lipids that come from the liver, ***(Wild, 1991)***.

Very low density lipoproteins (VLDL) are the second largest; they are produced mostly in the liver. They transport the endogenously produced TGs. Low density lipoprotein (LDL) originate from the intravascular metabolism of VLDL and are smaller and denser than VLDL particles. Their core contains mainly cholesterol esters thus serving the principle circulating source of cholesterol ***(Brown ct al., 1976).***

High density lipoproteins (HDL) are the smallest lipoprotein particles mid originate in the liver, small intestine and from the vascular denovo synthesis. Their core contains cholesterol esters and they have a critical role in reverse transport of cholesterol from peripheral tissue lo

the liver for elimination. The role of the lipids transported by lipoprotein particles is determined by both intravascular and intracellular mechanisms. In the intravascular compartment, lipoprotein metabolism depends on enzymatic reactions and the non-enzymatic transfer of lipids and apoproteins between different lipoprotein classes ***(Wild, 1991)***.

Three enzymes have a major role in intravascular lipoprotein metabolism:

1. Tissue lipoprotein lipase (LPL): is present in fat tissue, muscle, lung and lactating breast tissue, all of which can store free fatty acids or use them as an energy source. It hydrolyzes the fatty acid ester bond of the TG at positions 1 and 3 and free fatty acids (FFA) , so it is produced diffuse into adjacent cells for storage or use. This enzyme provides the rate limiting step for clearance of FFA from the circulation, it's synthesis and activity is regulated closely by plasma hormones.

2. Hepatic lipase (HL): is found in the liver sinusoidal epithelium and is synthesized only by the liver. Unlike (HL), it hydrolyzes the ester bond of both TG-rich lipids and phospholipids. It participates in the final processing of TG-rich lipoproteins and HDL cholesterol and was shown to be correlated negatively with plasma HDL cholesterol levels.

3. Lecithin-cholesterol actyl transferase (LCAT): it provides the only mechanisms for intravascular esterification of cholesterol and thus plays a major and beneficial role in reverse transport of cholesterol from the periphery to the liver ***(Wild & Aplebaum et al., 1990).***

The lipoprotein particles interact with special receptors on peripheral cell membranes that recognize particles and aid in clearance from the circulation. The dynamics of one such receptor, the LDL-cholesterol receptors was described by Brown and Goldstein ***(Brown ct al., 1976)***.

These receptor lipoprotein interactions are regulated not only by lipid supply and demand but also by various steroids and peptide hormones. Most of the removal of LDL cholesterol from plasma is mediated by the LDL receptor find have place primarily in the liver. Macrophage in circulation plays an important role in the uptake and oxidation of LDL and is important in the formation of atherogenic plaques ***(Wild & Guib et al., 1990).***

Effect of hormones on lipid metabolism:

1- Steroid hormones:

The net effect of estrogen is to : (a) Reduce LDL-cholesterol in serum, this is believed to be mediated by up-regulation of LDL receptors by estrogen . (b) Elevation of HDL-cholesterol which may be the result of enhancement of VLDL to HDL conversion by transfer of surface components, ***(Behrmann al., 1998).***

Synthetic progestins generally have the opposite effect by increasing LDL and lowering HDL. Progestins may interfere with estrogen activity by decreasing estrogen receptor number and antagonizing estrogen induced liver VLDL production and HDL-cholesterol formation ***(Knopp et al., 1982).***

Derivatives of 19-nortestosterone (e.g., norethidione and levonorgesterol) have greater effect on lipid metabolism than 17-hydroxyprogesterone derivatives (e.g. medroxy progestrine acetate). The former can reduce TG and VLDL, whereas the latter compounds do not cause this effect, ***(Knopp et al., 1982).***

Exogenous and endogenous corticosteroids and excess endogenous glucocorticoids stimulate adipocyte lipase activity and augment insulin action leading to increased hepatic TG and VLDL synthesis. They stimulate LDL activity to increase conversion of VLDL to LDL cholesterol; this often leads to hypercholesterolemia. The net effect of corticosteroids is to increase cardiovascular risk ***(Wild, 1991).***

**** Effect of androgens on lipid metabolism:**

Like progestins, exogenous androgens increase plasma LDL-cholesterol by increasing ML activity, enhancing VLDL-cholesterol catabolism by liver and down regulates LDL receptors. Exogenous androgenic steroids enhance TG removal by the liver and inhibit VLDL-cholesterol and TG production, **(*Pasquali et al., 1991)***.

The altered estrogen-androgen ratio with relatively androgen excess is associated with detrimental changes in lipid metabolism in terms of cardiovascular risk. The rate of cardiovascular morbidity and mortality in postmenopausal women rises significantly over the premenopausal rate and become similar to that of men ***(Wild ct al., 1991).***

Hyperandrogenism is associated with upper body obesity expressed as waist hip ratio (WHR) independently of weight . Furthermore, administration of exogenous androgen to women leads to increase visceral fat accumulation, **(*Pasquali et al., 1991).***

However the mechanisms of androgen actions on lipid metabolism are still poorly understood There is growing evidence that androgens may influence the predominant site of body fat deposition and muscle morphology, possibly in relation to alteration in insulin metabolism and sensitivity . Androgens may adversely affect lipid metabolism by direct modulation of lipoprotein lipase and lipolysis ***(Rebuffe et al., 1988).***

The effect of androgen on lipid profile may be sex dependent. Studies in hypogonadal men are inconsistant and indicate that androgen replacement may have either an adverse or a beneficial effect ***(Rebuffe et al., 1988).***

Increasing androgenicity, as reflected by decrease in SHBG and increase in free testosterone was accompanied by a-Increase WHR, this relationship being independent of and additive to that of obesity level. b-Increase size of abdominal but not femoral adipocytes. c-Increase plasma glucose and insulin level. d- Diminished insulin sensitivity ***(Evans et al., 1983).***

The rise in testosterone concentration at puberty in boys is associated with a decrease in HDL-cholesterol concentration ***(Wild, 1991)***.

There is some evidence that in men testosterone is a key factor regulating HDL levels and composition **(*Goldberg ct al., 1985)***.

2-Peptide hormones:

Insulin increases LPL synthesis and activity, particularly in fat cells. The net effects of endogenous or exogenous insulin excess is to increase circulating FFA specially in portal circulation; this may be an

important factor in the development of insulin resistance ***(Beviacqua et al., 1987).***

Insulin resistance leads to TG elevation. This effect is found mostly in centripetal obesity because intra-abdominal fat is high in lipolytic activity compared with peripheral fat where the antilipolytic effect of insulin is less effective. This less effect may be the result of reduced insulin receptor binding ***(Wild, 1991).***

Glucagon stimulates intracellular lipase and prevents intracellular accumulation of FFA in fat cells. Thyroid hormone acts in concert with insulin to increase LPL activity. In normal studies, prolactin was shown to inhibit LPL activity, ***(Wild, 1991).***

Relationship between hyperandrogenism, insulin resistance, dyslipidemia and obesity:

There is a close relationship between these variables (Wild, 1991). The relation between insulin resistance, especially overt diabetes mellitus and dyslipidemia is well established. Upper body "android obesity" (UBO) is closely associated not only with insulin resistance, but also with increased cardiovascular risk. PCOS is associated with UBO , insulin resistance and hyperandrogenism. UBO is related to coronary artery disease, diabetes, hypertension and dyslipidemia **(*Wild, 1991).***

Increased waist-hip ratio (WHR) was associated with decreased glucose tolerance, HDL-cholesterol and increased TGs. The WHR also positively correlates with blood pressure and total plasma cholesterol. Associated with hyperinsulinemia, UBO is at least in part a result of reduced hepatic extraction of insulin. Adipocytes from upper body adipose tissue have unique characteristics compared with peripheral

adipocytes. Their cell volume is larger and has a higher rate of basal and epinephrine-stimulated lipolysis. Abdominal adipocytes are more resistant to the antilipolytic effect of insulin. The anatomic location of visceral fat facilitate a higher exposure of the liver to FFA. The increase in plasma FFA is most pronounced at night. Also there are marked regional differences in the ability of adipose tissue to convert androgen to estrogen or their 5 α reduced products. With UBO, there is less conversion of androstenedione to estrone than with lower body obesity.

With increased exposure to unbound androgens, abdominal adipocytes have increased lipolysis and plasma FFA. Elevated FFA contribute to reduced hepatic insulin extraction and hyperinsulinemia. They inhibit peripheral glucose metabolism and diminish insulin responsiveness. Increased FFAs also inhibit estcrification of cholesterol in HDL cholesterol particle. This decrease the efficacy of cholesterol removal by HDL, from the periphery to the liver. In addition VLDL cholesterol synthesis increase with an increasing FFA load, this leads to hyperglyceridemia **(*Wild, 1991).***

In PCOS hyperandrogenic activity is common, these patients also have increased cholesterol, TG, LDL plasma level and decrease HDL level than control subjects **.** Altered lipids in hyperandrogenic women may result from independent effect of androgen and insulin ***(Wild et al., 1990).***

Suppression of plasma testosterone by GnRH agonist in hyperandrogenic women was shown to cause minimal alteration in lipid and apolipoprotein profiles when given for 3 months **(*Wild, 1991).***

Insulin sensitivity was not changed during GnRH agonist administration in this study. This suggest the independent effect of insulin

on lipid metabolism. Correlation between fasting insulin and lipid profile alteration become stronger after gonadal influence was removed, however this suggests that the effect of insulin resistance may be stronger than the independent effect of endogenous androgen. However, hyperandrogenicity in women with PCOS are of heterogenous mechanisms and there may be different sources of androgen secretion ***(Wild et al., 1991).***

Although insulin stimulates TG metabolism and hepatic VLDL-cholesterol secretion, endogenous testosterone may alter HDL cholesterol through apoprotein A-l compartment. Insulin, either through a direct effect on the ovarian theca cell, the insulin growth factor and/or its own receptors, increases ovarian androgen production. Insulin also potentiates the effect of LH on ovarian stromal androgen production. The hyperinsulinemia of various syndromes of insulin resistance is announced with hyperandrogenism**.** In granulosa cells in vitro , insulin stimulates cytochrome P450 side chain cleavage activity**,** fascilitates FSH induction of LH receptors, and enhances estrogen and progesterone biosynthesis ***(Boranao et al., 1984).***

Furthermore, insulin stimulates human ovarian stromal androgen production and an administration of an insulin infusion in hyperandrogenic women produces an acute rise in the serum androstenedione concentration, ***(Barbieri et al., 1986)***.

A good correlation between insulin and BMI was found in normal and obese women without hormonal dysfunction and in patients with or without PCOS. Insulin, androgens and BM1 arc related in women both with PCOS and without PCOS especially in obese ones. Insulin and metabolic indices were similar in lean women with PCOS and those

without PCOS , but obese women with PCOS arc more insulin resistant, hyperandrogenic and hypertriglyceridemic ***(Ancien P. et al., 1999 July)***

Three hypothetical mechanisms were proposed to explain the association between UBO, hyperandrogenism, hyperinsulinemia and dyslipidemia *(Bjorntrp et al., 1988).*

In the first mechanism, UBO was the underlying condition that led to diabetes, hypertension and lipid aberrations. Abdominal adipose tissue has high lipolytic activity and responds less to the antilypolytic effects of insulin. The resulting increase in serum FFA leads to decreased glucose transport, insulin resistance and hyperinsulinemia. Increased serum FFA also leads to increased secretion of VLDL through FFA effects on the liver. This ultimately leads to increased serum cholesterol and TG. Hyperinsulinemia also may contribute to the pathophysiology of hypertension, ***(Bjorntrp et al., 1988)***.

In the second mechanism, UBO is one of several consequences of increased adrenal activity, reflected in increased adrenal cortisol and androgen which promote the development of abdominal obesity, which then leads to insulin and lipid disorders as described. In addition, when adrenal activity is increased, muscle fiber composition changes to higher proportion of type 2 white, fast-twitched fibers that are less insulin sensitive than the red slow twitched variety. Therefore insulin resistance is the result of increased muscle and adipose tissue resistance.

In the third mechanism, hypothalamic arousal secondary to stress results in elevated sympathetic activity and leads to hypertension. Elevated corticotrophin causes increased adrenal cortisol and androgens, which in turn contribute to abdominal obesity, insulin resistance and

elevated serum FFA. Alteration in LH/FSH ratio are a result of hypothalamic dysfunction, leading to reduced progesterone and this contributes to android obesity ***(Wild, 1991).***

It is known that both endogenous and exogenous sex steroids are capable of altering cholesterol, triglycerides and lipoprotein levels in serum **(*Ancien et al., 1999)***

Studies included 114 women of reproductive age in a cross-sectional study to demonstrate the fluctuation in serum lipid during the menstrual cycle. The study showed a significant decrease in total cholesterol and phospholipids during the luteal phase. The LDL cholesterol decreased during the luteal phase and VLDL cholesterol increased in the early and mid luteal phases. The LDL phospholipid and VLDL-triglycerides also showed a significant decrease during the luteal phase , ***(Dror Mcirow et al., 1996).***

The overall data suggest that the changes in cholesterol, triglycerides and phospholipids during the menstrual cycle of women reproductive age are influenced by endogenous hormonal changes.

Dyslipidemia with PCOS

Women with PCOS have disturbed lipoprotein lipid profile. Android type obesity is present in 40-50% of the patients **(*Dror Meirow et al., 1996)*** .

Hyperandrogenism with higher circulating concentration of testosterone, androstenedione, dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) are common features and result phenotypically in hirsutism, acne and oily skin ***(Yen, 1980)***.

Circulating blood concentrations of adrenal androgen DHEA-S are raised in 50% of PCOS patients ***(Hoffman et al., 1984)***.

Metabolic tests have shown that testosterone in men is closely involved in high density lipoprotein (HDL) regulation **(*Goldberg et al., 1985)*** while women with excess of androgen have an atherogenic lipoprotein profile **(*Wild, 1991; Sowers, 1992)***.

Low DHEA-S concentrations are associated with high concentrates of HDL ***(Leszczynski et al., 1989, Nestler et al., 1992)*** and epidemiological studies have shown an inverse relationship between DHEA-S and ischemic heart disease **(*Dunaif et al., 1990)***.

Hyperandrogenism and insulin resistance are closely related ***(Stuart et al., 1987; Nader, 1991)***.

When hyperandrogenism is present in PCOS patients, it may be the primary reason for dyslipidemia, which is more pronounced in overt diabetes ***(Reaven, 1988)***.

Insulin lowers DHEA-S blood concentration by inhibiting synthesis and increasing catabolism ***(Nestler et al., 1992).***

PCOS patients have dyslipidemia and disturbed lipid profile when divided into insulin sensitivity and non insulin resistance. It was found that in insulin sensitivity group, insulin and DHEA-S were positively correlated with total cholesterol, LDL and TG and negatively with HDL. In non IR group insulin was not related to any of the lipids and DHEA-S was negatively related to cholesterol and LDL. Thus dyslipidemia in PCOS may occur irrespective of insulin sensitivity and may have

different metabolic etiologies depending on DHEA-S metabolism, ***(Dror Mcirow et al., 1996).***

Another study was made to investigate the relationship between androgen excess, insulin sensitivity and altered lipoprotein lipids in PCOS,it suggests that altered lipid profiles in women with PCOS may result from the independent effects of androgen excess and insulin sensitivity **(*Wu X. et al., 1998).***

Other studies showed a positive correlation between triglyceride levels and levels of free and total testosterone and a negative correlation between HDL cholesterol levels and total and free testosterone ***(Senoz et al., 1994)***.

The exact mechanism causing this dyslipidemia is not exactly known. Although total and free testosterone and DHEA-S levels were higher in patients with PCOS than in controls; no strong correlation was found between androgen levels and lipoprotein levels ***(Wild et al., 1985).***

Other authors ***Senoz 1994***, positively correlated between triglyceride levels and androgen levels. In an interesting study of ***Norman et al 1995,*** a group of 118 women showing PCOS on vaginal ultrasound scan was divided into those who had no hyperandrogenemia (n=21) and those with increased androgen and a clinical presentation normally associated with PCOS (n=97). These were compared with a reference group of 26 normal subjects. Glucose intolerance, lipid concentrations and endocrine profile were compared between groups. It was stated that subjects with PCOS ovaries without hyperandrogenemia exhibit similar disturbances in insulin and lipid profiles as those with PCOS ***(Senoz et al., 1994)***.

A study was made to examine the influence of hyperandrogenism on low-density lipoprotein (LDL) and high density lipoprotein (HDL). It was found that hyperandrogenemia may have an adverse effect on serum lipopeoteins through effects on HDL. Hispanic women may have a higher level of the atherogenic lipoprotein phenotype b, which may increase their risk for atherosclerosis ***(Legro et al., 1999).***

On the other hand a study was made to investigate the effect of a pure antiandrogen receptor blocker, flutamide, on the lipid profile in PCOS women. The primary outcome was the change in the ratio of low density lipoprotein (LDL) to high density lipoprotein (HDL). Treatment with flutamide was associated with a significant decrease in the HDL/LDL ratio by 23%, in total cholesterol by 18%, in LDL by 13% and in TGs by 23%. Flutamide treatment was also associated with a trend toward an increase in HDL by 14%. The effects on lipid profile were found regardless of obesity and .were not associated with a change in weight. Furthermore, actions of flutamide on lipid metabolism were not associated with significant changes in circulating adrenaline or noradrenaline, glucose metabolism nor insulin sensitivity. This report has demonstrated for the first time that treatment with the pure antiandrogen, flutamide may improve the lipid profile and that this effect may be due to direct inhibition of androgenic actions ***(Diamenti-Kandarakis et al., 1998.)***

A study on twines comparing polycystic ovary syndrome and lipid profile was carried out to assess the relative contribution of genetic and environmental factors (particularly androgens) on circulating levels of lipid fractions and to determine the effect. A group of 19 monozygotic and 15 dizygotic twin pairs were identified and ultrasound, clinical and biochemical parameters were used to do fine polycystic ovaries. Serum

androgen and lipid fractions were also measured. Eleven pairs of the twins (5MZ, 6DZ) were scanned discordant (one twin had polycystic ovaries and the co-twin did not). Serum levels of the lipoprotein fractions in twins with polycystic ovaries were not significantly different from the levels found for their co-twins with normal ovaries. There were no significant correlations between androgen related hormone and any of the lipid measurements. Body mass index (BMI) was positively correlated with TGs and lipoprotein (LDL) and negatively correlated with HDL-cholesterol. Sex hormone binding globulin levels were negatively correlated with TGs and LDL and positively associated with HDL-C. Fasting insulin levels were significantly correlated with TGs and negatively with HDL-C. This means that twins discordant for the PCOS do not have significantly different lipid fractions ***(Jahanfar et al., 1995).***

However, because many PCOS patients are obese and obesity is known to influence lipoprotein lipids, the influence of body weight on lipoprotein lipids in PCOS patients have been studied by Robert A Wild and his co-workers. They evaluated 13 PCOS patients with ideal body weight; They found elevated levels of cholesterol, triglyceride, VLDL and low level of HDL compared with their 13 control matched group. Results of the study suggest that excess weight alone does not readily explain the dyslipidelmia observed in PCOS patients, ***(Wild et al., 1988)***.

On the other hand, other authors regard obesity as the cause of dyslipidemia in PCOS, ***(Rojanasakul et al., 1988)***. In this study of 54 PCOS patients were divided into three groups according to body mass index (non obese '27', overweight '13' and obese '14'), all groups had a similar age and height, All three groups of patients with different BMI had similar hormonal profiles of PCOS which were different from the control. The dyslipidemia in form of elevated levels of cholesterol,

triglyceride, LDL and decreased HDL was markedly observed only in the obese group, ***(Rojanasakul et al. 1988)***.

However, the alteration of lipid metabolism in these patients could not be ascribed to PCOS because the patients and the control were not of similar body weight ***(Rojanasakul et al., 1988).***

Androgens influence serum lipids and lipoproteins. In PCOS, beside the androgen excess, estrogen level is also altered ***(Franks et al., 1985).***

There is cyclic estrogen production. Serum E_2 are comparable with those in normal women during the early to mid-follicular phase. Serum E_2 is also higher than normal. SHBG in PCOS patients is low ***(Lobo et al., 1996)***. This results in higher levels of free E_2 as well as androgen. Women with PCOS arc therefore in a functional hyperestrogenism status. Estrogen and androgen have the opposite effects on some lipids and lipoproteins Therefore the alteration of estrogen production in PCOS might balance the effect of androgen on serum lipids and lipoproteins ***(Kajahasakul et al., 1988)***

There were no significant differences in lipid measurements between the obese and non-obese PCOS patients except FFA levels, which were higher in obese subjects ***(Rajkhowa et al., 1997).*** However, they correlated that obesity has an important influence. Obese PCOS and control subject had higher levels of cholesterol, triglyceride and fatty acids than their lean counterparts. The obese women with PCOS had markedly increased plasma FFA concentration. This may be due to the increased truncal-abdominal fat mass, with a higher lipolytic activity ,

and a generally impaired insulin suppression of FFA release from adipose tissue in the insulin resistant slate, ***(Martin et al., 1990).***

Furthermore, the observed association between plasma FFA and testosterone suggests that recently established effect of testosterone in fascilitating FFA release from abdominal fat tissue could be of importance in women with PCOS. FFA levels were inversely associated with insulin sensitivity in the women with PCOS and with glucose tolerance, ***(Rebuffe et al., 1988)***.

Elevated FFA levels may interfere with peripheral glucose uptake , and with the action of insulin on hepatic glucose production, together with the recently reported strong association between truncal-abdominal obesity and insulin resistance in women with PCOS, the present findings suggest a role for fatty acid metabolism as a link between these abnormalities, (***Holte et al., 1994)***,.

Relation between Plasma Leptin, Obesity and PCOS:

It has been reported that plasma leptin levels in obese women with PCOS were significantly higher than those lean healthy women. A significant positive correlation between plasma leptin and BMI and between leptin and testosterone in women with PCOS . Plasma NPY levels were significantly elevated in both non-obese and obese women with PCOS. However, in obese non-PCOS women plasma NPY levels gradually increased with increase in BMI. In obese women with PCOS, plasma leptin is increased compared with lean women. Serum insulin concentration is increased in obese women with PCOS. A positive correlation exists between leptin and BMI as well as between leptin and testosterone in women with PCOS. These results may suggest that the

feedback system in the interaction between leptin and NPY is disturbed in PCOS ***(Barana, Ociska et al., 1999.).***

Effects of insulin and insulin like growth factors on ovarian steroidogenesis

Investigations as those of **Baranao and Hammond ,** suggested that many other proteins may play major roles in ovarian folliculogenesis and steroidogenesis. The emerging consensus is that insulin and insulin like growth factors exert important effects on ovarian functions. Insulin belongs to a group of growth factors with similar biochemical characteristics. The family of IGFs includes insulin, IGF-I (somatomedin C), IGF-II (somatomedin A), nerve growth factor and relaxin, ***(Baranao and Hammond 1984),***.

Actions of insulin and insulin like growth factors:

Insulin has been found in follicular fluid of some but not all patients. Whether it was secreted or sequestrated has not been demonstrated. It was found to correlate with follicular fluid progesterone levels but not with estradiol or androstenedione ***(Diamond ct al., 1985)***.

Also recent evidence suggests that insulin, IGF I and IGF II might be important regulators of thecal and stromal androgen production. This action might be mediated through the following;

1. Inducing functional activities of P 450.

2. Augmenting the ability of LH to induce P 450 and 17-hydroxylase /C 17-20 lyase activities in the theca interstitial cells ***(Barbieri et al., 1983)***.

Some of these effects of insulin may be indirect and mediated by the decrease of hepatic secretion of IGF-BPI with an increase in the activity of circulating IGF-1 on the ovary leading to stimulation of androgen secretion ***(Bregen et al., 1993)***, increase the binding of LH to its ovarian receptors and activate the coenzyme P450,C17, ***(Cara et al., 1988)***.

Moreover, IGF-I may be responsible for some of the morphologic alterations of PCOS, altering the balance between follicular growth and follicular atresia ***(Carmina et al., 1996)***.

Follicular fluid insulin and progesterone are positively correlated and that the enhanced pituitary hypothalamic LH secretion induces a switch in the theca cell function from an androgen to a progesterone secreting tissue. High levels of progesterone are shown to have an inhibiting effect on oocyte maturation and this whole process also leads to a reduced follicular estrogen and ultimately follicular atresia, (***Diamond et al.,1985)***,.

The sequence of events in hyperinsulinemic hyperandrogenism:

There are several studies which indicate that hyperinsulinemia produces hyperandrogensim and not the reverse :

- The administration of insulin to women with PCOS increase circulating androgen levels ***(Elkind-hirsch et al., 1991).***

- The administration of glucose to hyperandrogenic women increase the circulating levels of both insulin and androgens ***(Smith et al., 1987)***.

- Weight loss decreases the levels of both insulin and androgens ***(Kiddy et al., 1989)***.

- In vitro, insulin stimulates thecal cell androgen production ***(Barbieri et al., 1986)***.

- The experimental reduction of insulin levels (using dioxide) in women with PCOS reduces androgen levels employed an analogue of somatostatin, ***(Prelevic et al.1990)***,.

- ***Dunaif and Graf (1989)*** demonstrated that these acute rises in androgen levels following glucose stimulated insulin release in women with PCOS are independent of any change in LH secretion.

- After normalization of androgens with GnRH agonist treatment, the insulin response lo glucose testing remains abnormal in obese women with PCOS ***(Dahlgreen et al., 1992).***

The role of obesity:

Overweight anovulatory PCOS women with hyperandrogenism have a characteristic distribution of body fat known as android obesity. Android obesity is the result of fat deposited in the abdominal wall and visceral mesenteric region. This fat is more sensitive to catecholamines, less sensitive to insulin and more active metabolically. This fat distribution is associated with hyperinsulinemia, impaired glucose tolerance, diabetes mellitus and an increased androgen production rates ***(Pasquali et al., 1993).***

Hyperinsulinemia and hyperandrogenism, however are not confined to anovulatory women who are overweight, it is important to note that the combination of increased androgen secretion and insulin resistance has been reported in both obese and non obese anovulatory women ***(Morales ct al., 1996).***

For this reason, some have suggested that hyperandrogenic women with polycystic ovaries could be divided into two groups: those with obesity, insulin resistance, hyperinsulinemia and normally or minimally elevated LH levels; those with elevated LH levels have no insulin resistance and normal insulin levels ***(Dahlgreen et al., 1992).***

Hyperinsulinemia and hyperandrogenism are not explained, therefore solely by obesity and specifically android obesity. However the presence of obesity adds the insulin resistance and hyperinsulinemia associated with obesity to that which is specifically unique to the anovulatory polycystic ovary state **(*Jahanfar et al., 1995).***

In obese insulin resistant women, caloric restriction that results in weight reduction will reduce the severity of insulin resistance (a 40% decrease in insulin level with a 10 kg weight loss), this decrease in insulin levels would result in marked decrease in androgen production (a 35% decrease in testosterone level with a 10 kg weight loss) ***(Kiddy et al., 1992).***

Metabolic, Cardiovascular, and

Other Clinical Complications with PCOS

The consequences of the polycystic ovary syndrome extend beyond the reproductive axis; women with the disorder are at substantial risk for the development of metabolic and cardiovascular abnormalities similar to those that make up the metabolic syndrome, (***Glueck et al; 2003).***

This finding is not surprising, since both the polycystic ovary syndrome and the metabolic syndrome share insulin resistance as a central pathogenetic feature. The polycystic ovary syndrome might thus be viewed as a sex-specific form of the metabolic syndrome, ***(National Cholesterol Education Program; 2002)***, and the term "syndrome XX" has been suggested as an apt term to underscore this association, **(Sam et al; 2003)**.

Obesity:

Obesity is present in at least 30 percent of cases; in some series, the percentage is as high as 75, ***(Azziz et al; 2001).***

Women in the United States with the polycystic ovary syndrome generally have a higher body weight than their European counterparts, ***(Azziz et al; 2001 , Carmina et al; 2003).***

This fact has been cited as an explanation for the increase in the incidence of the polycystic ovary syndrome in the U.S. population — an increase that parallels the increase in obesity***, (Mokdad et al; 2001).***

Increased adiposity, particularly visceral adiposity that is reflected by an elevated waist circumference (>88 cm [35 in.]) or waist-to-hip ratio, has been associated with hyperandrogenemia, insulin sensitivity, glucose intolerance, and dyslipidemia, Attenuation of insulin sensitivity, whether accomplished by weight loss or with medication, ameliorates (but not

necessarily normalizes) many of the metabolic aberrations in women with the polycystic ovary syndrome. ***(National Cholesterol Education Program; 2002)*** .

Impaired Glucose Tolerance and Type 2 Diabetes

Thirty to 40 percent of women with the polycystic ovary syndrome have impaired glucose tolerance, and as many as 10 percent have type 2 diabetes by their fourth decade, (***Ehrmann et al; 1999 , Legro et al; 1999).***

These prevalence rates are among the highest known among women of similar age, ***(Krosnick et al; 2000).***

An enhanced rate of deterioration in glucose tolerance is also evident in the PCOS, (***Ehrmann et al; 1999***. ***Norman et al; 2001).***

Semilar studies by Dunaif et al. indicated that women with the polycystic ovary syndrome are more insulin resistant than the unaffected counterparts matched for body-mass index, fat-free body mass, and body-fat distribution. A defect in the insulin signaling pathway appears to be present in both the adipocyte and skeletal muscle, the primary target tissues of insulin action, ***(Dunaif 1997 , Dunaif et al; 2001).***

Insulin resistance alone cannot fully account for the predisposition to and development of type 2 diabetes among patients with the PCOS. In patients with normal glucose tolerance, insulin secretion is (by definition) sufficient for the degree of insulin resistance; when the pancreatic βcell is no longer able to compensate sufficiently, glucose tolerance begins to deteriorate, ***(Kahn et al; 1993 , Polonsky et al; 1996).***

Most women with the PCOS are able to compensate fully for their insulin resistance, but a substantial proportion (particularly those with a first-degree relative with type 2 diabetes) have a disordered and insufficient β-cell response to meals or a glucose challenge, (***Ehramann et al; 2002 , Ehramann et al; 2004)***.

Before the development of frank glucose intolerance, defects in insulin secretion may be latent and revealed only in circumstances that augment insulin resistance, as with the development of gestational diabetes in pregnancy, ***(Kousta et al; 2000)***, or glucose intolerance associated with glucocorticoid administration, (***Ehrmann et al; 2004)***.

Hypertension and Vascular Dysfunction

Hypertension develops in some women with the PCOS during their reproductive years, (***Gluek et al; 2003),*** and sustained hypertension may develop in later life in women with the disorder, ***(Dahlgren & Johansson et al; 1992).***

Reduced vascular compliance, (***Kelly et al; 2002)***, and vascular endothelial dysfunction were noted in most, (***Kelly et al; 2002 , Paradisi et al; 2003 , Orio et al; 2004***), but not all ***(Mather et al; 2000),*** studies of women with the PCOS.

Furthermore, the degree of impairment in vascular reactivity is significantly greater than can be explained by obesity alone, ***(Kelly et al; 2002).***

Insulin-lowering therapies appear to improve the vascular endothelial dysfunction in patients with the PCOS, ***(Paradisi et al; 2003).***

Coronary and Other Vascular Disease

A predisposition to macrovascular disease and thrombosis in women with the PCOS has also been described, ***(Yildiz et al; 2002 , Orio et al; 2004).***

A recent study of premenopausal women showed that those with the PCOS had a higher prevalence of coronary-artery calcification as detected by electron-beam computed tomography, ***(Christian et al; 2003).***

Incr**ease**d levels of plasminogen-activator inhibitor type 1 may contribute to this risk, ***(Ehramann et al; 1997 , Atiomo et al; 1998).***

Levels of plasminogen-activator inhibitor type 1 in patients with the PCOS may exceed those typically seen in type 2 diabetes, ***(Ehramann et al; 1997).***

A reduction in insulin levels decreases levels and activity of plasminogen-activator inhibitor type 1, ***(Ehramann et al; 1997).***

Hypertriglyceridemia, increased levels of very-low-density lipoprotein and low-density lipoprotein cholesterol, and decreased levels of high-density lipoprotein cholesterol also predispose patients to vascular disease in the PCOS. Both insulin resistance and hyperandrogenemia contribute to this atherogenic lipid profile, ***(Talbott et al; 1995).***

Testosterone decreases lipoprotein lipase activity in abdominal fat cells, and insulin resistance impairs the ability of insulin to exert its antilipolytic effects. Although these abnormalities would be expected to increase the morbidity and mortality from coronary artery disease and

other vascular disorders in women with the PCOS, this has been difficult to establish, ***(Wild et al; 2003, Legro et al; 2003 , Talbott et al; 2004).***

Obstructive Sleep Apnea

Recent studies indicate that the prevalence of obstructive sleep apnea in the PCOS is higher than expected and cannot be explained by obesity alone, the severity of sleep apnea did not correlate with body-mass index; even after controlling for body-mass index, the risk of sleep-disordered breathing was increased by a factor of 30. Insulin resistance appears to be a stronger predictor of sleep-disordered breathing than is age, body-mass index, or the circulating testosterone concentration, ***(Fogel et al; 2001 , Gopal et al; 2002)***

Association with Cancer

There is an increased prevalence of endometrial hyperplasia and carcinoma in women with the PCOS, ***(Balen et al; 2001 , Hardiman et al; 2003).***

This increase has been attributed largely to the persistent stimulation of endometrial tissue by estrogen (mainly estrone) without the progesterone-induced inhibition of proliferation and differentiation to secretory endometrium that occurs after ovulation. Endometrial carcinoma has also been associated with obesity and type 2 diabetes, both of which are common in the PCOS ***(Balen et al; 2001 , Hardiman et al; 2003).***

Breast and ovarian cancer have been variably associated with the polycystic ovary syndrome; obesity, anovulation, infertility, and the hormonal treatment of infertility are so frequent in the PCOS at the

condition is difficult to isolate as an independent risk factor for these types of cancer, ***(Balen et al; 2001).***

Introduction

Insulin sensitivity in PCOS appears to be independent of, but is amplified by, obesity ***(Holte et al 1994, Morales et al 1996)***.

Recently, several laboratories have investigated the cellular mechanism(s) underlying insulin sensitivity in PCOS employing a

classical insulin target tissue, isolated adipocytes. The most striking common finding in these studies was a large reduction in insulin sensitivity for glucose transport stimulation in the face of normal insulin binding. Thus, insulin sensitivity in PCOS represents postbinding defects in signal transduction ***(Dunaif et al 1992, Marsden et al . 1994).***

Definition of Insulin Resistance

Insulin resistance is defined as reduced hyperglycemic response to a given amount of insulin. Only recently was it realized that mild hyperinsulinemia and insulin resistance are common findings in PCOS ***(Pasquali et al., 1983)*** and that a derangement of insulin secretion may represent a main component of the pathogenesis and the clinical expression of the syndrome ***(Dunaif et al., 1995).***

Incidence of insulin resistance & hyperinsulinemia in PCOS women:

Insulin resistance occurs not only in obese women with PCOS where it might be expected because obesity is often associated with insulin resistance but also in 50% of normal weight women with PCOS

(Buyalas et al., 1996). In those patients, fasting serum insulin levels are higher when compared to controls of the same body weight. The overall prevalence of documented insulin resistance is approximately 70%-75% in PCOS women patients ***(Conway et al., 1990).***

Types of insulin resistance

There are three broad categories of insulin resistance:

- Type A insulin resistance: is characterized by either a decreased number of insulin receptors or a decreased functional capacity of the receptors. It is often due to genetic defect which in many individuals could be demonstrated at a young age.

- Type B insulin resistance: is due to circulating antibodies to insulin receptors. This type of insulin resistance is often associated with autoimmune diseases being apparent in adulthood.

- Type C insulin resistance: is due to post receptor defects. Obesity is often associated with type C or type A insulin resistance, ***(Khan 1976)***.

Although type A and B insulin resistance are due to different molecular mechanisms, both resulted in hyperinsulinemia and hyperandrogensim. The observation that two genetically different causes of insulin resistance both resulted in hyperandrogensim prompted to pursue the possibility that hyperinsulinemia causes hyperandrogenism.

The basic hypothesis is that both insulin and LH regulate ovarian stromal and thecal production ***(Taylor et al., 1982)***.

Glucose and glucose tolerance in PCOS

Glucose appearing in the blood after a meal is derived from glucose absorbed by the intestine and glucose produced by the liver. In response to the rise in blood sugar, an adequate amount of insulin is secreted to maintain euglycaemia, suppressing endogenous glucose production (***Ferrannini & Groop 1989),*** and increasing glucose uptake in the skeletal muscle ***(Mandarino et al. 1987).***

In peripheral tissues, glucose is utilised either by the oxidative or the non-oxidative pathway . In muscle tissue, oxidation of glucose yields CO2 and water and the formation of adenosine triphosphate (ATP), while the non-oxidative pathway comprises glycogen synthesis, lipogenesis and anaerobic glycolysis, i.e. formation of lactate and alanine. During hyperinsulinaemia, glycogen synthesis predominates and it has been shown to account for virtually all non-oxidative glucose metabolism ***(Schalin-Jäntti 1995).***

Increased glucose levels during an OGTT have been shown in obese PCOS women, but not in non-obese PCOS women, compared with age- and weight-matched ovulatory hyperandrogenic and control women ***(Dunaif et al. 1987).***

Twenty to forty per cent of women with PCOS screened by means of an OGTT show impaired glucose tolerance (***Dunaif et al. 1992, Dunaif & Finegood 1996, Dunaif 1997).***

Recent studies have suggested that the conversion of IGT to type 2 diabetes mellitus (DM) is 5- to 10-fold accelerated in women with PCOS, especially in those with obesity and a family history (FH; first-degree relative) of type 2 DM (***Ehrmann et al. 1999).***

As fasting glucose seems not to be a reliable predictor of the B-glucose concentration at 2 hours (used for the diagnosis of IGT during an OGTT), OGTTs have been recommended for all women with PCOS at the time of diagnosis and yearly thereafter (***Ehrmann et al. 1999).***

Weight reduction is important in treating overweight patients with the polycystic ovary syndrome. No unique weight-loss regimen targets excess adiposity specific to the syndrome. Restricting carbohydrates as compared with fats is generally perceived to be advantageous in this patient population. However, several recent studies designed to address this issue have not shown a distinct benefit from calorie-restricted diets limiting carbohydrates rather than fat, ***(Moran et al 2003 , Stamets et al 2004)***

FIGURE " 2 "

A reduction in insulin levels pharmacologically ameliorates sequelae of both hyperinsulinemia and hyperandrogenemia. The place of insulin-reduction therapies in treating the PCOS is evolving and should be viewed in context with all available therapies. These therapies can effectively manage the established metabolic

derangements in the PCOS, but whether they can prevent them is not yet established, (***(Moran et al 2003 , Stamets et al 2004)***

Both metformin (a biguanide) and the thiazolidinediones pioglitazone and rosiglitazone have been used to reduce insulin resistance. Although metformin appears to influence ovarian steroidogenesis directly, this effect does not appear to be primarily responsible for the attenuation of ovarian androgen production in women with the PCOS. Rather, metformin inhibits the output of hepatic glucose, necessitating a lower insulin concentration and thereby probably reducing the androgen production of theca cells, ***(Attia et al 2001 , Mansfield et al 2003).***

Subject characteristics and control measures for effects of weight change, dose of metformin, and outcome vary widely among published studies of metformin in the PCOS. A recent meta-analysis of 13 studies in which metformin was administered to 543 participants, ***(Lord et al 2003),*** reported that patients taking metformin had an odds ratio for ovulation of 3.88 (95 percent confidence interval, 2.25 to 6.69) as compared with placebo and an odds ratio for ovulation of 4.41 (95 percent confidence interval, 2.37 to 8.22) for metformin plus clomiphene as compared with clomiphene alone. Metformin also improved fasting insulin levels, blood pressure, and levels of low-density lipoprotein cholesterol. These effects were judged to be independent of any changes in weight that were associated with metformin, but controversy persists as to whether the beneficial effects of metformin are entirely independent of the weight loss that is typically seen early in the course of therapy, ***(Crave et al 1995).***

Finally, the rates of spontaneous miscarriage and gestational diabetes are reportedly lower among women with the PCOS who conceive

while taking metformin. The long-term effects of metformin in pregnancy are unknown, ***(Gluek et al 2001, Gluek & wang et al 2002, Gluek et al 2004)***

The thiazolidinediones improve the action of insulin in the liver, skeletal muscle, and adipose tissue and have only a modest effect on hepatic glucose output. As with metformin, ***(Attia et al 2001),*** the thiazolidinediones are reported to affect ovarian steroid synthesis directly, although most evidence indicates that the reduction in insulin levels is responsible for decreased concentrations of circulating androgen,(***Mitwally et al 2002).***

Obese women with the polycystic ovary syndrome who took troglitazone had consistent improvements in insulin resistance, hyperandrogenemia, and glucose tolerance***.(Dunaif et al 1996).***

In addition, troglitazone treatment was associated with a relative improvement in pancreatic β-cell function and a reduction in levels of the prothrombotic factor plasminogen-activator inhibitor type 1, ***.(Dunaif et al 1996).***

These findings led to a double-blind, randomized, placebo-controlled study of troglitazone in women with PCOS. Ovulation was

significantly greater for women who received troglitazone than for those who received placebo; free testosterone levels decreased, and levels of sex hormone–binding globulin increased in a dose-dependent fashion. Nearly all glycemic measures showed dose-related decreases with troglitazone treatment. Although troglitazone is no longer available, subsequent studies using rosiglitazone, ***(Chazeeri et al 2003, Belli et al 2004)***, and pioglitazone, (***Romualdi et al 2003)***, have had similar results. Because of

concern about using thiazolidinediones in pregnancy, the drugs have been less readily adopted for routine clinical use.

Controversies in evaluation of women with PCOS:

Several unresolved controversies persist regarding the evaluation and treatment of women with the PCOS. One issue surrounds the question of whether all women with the PCOS should be screened for glucose intolerance, insulin resistance, or both. Screening is supported by evidence that the combined prevalence of impaired glucose tolerance and type 2 diabetes approaches 45 percent by the fourth decade, that both impaired glucose tolerance and type 2 diabetes are associated with significant morbidity, and that there is a substantial rate of conversion from impaired glucose tolerance to diabetes in the absence of intervention among women with the polycystic ovary syndrome, and those without the condition, ***(Tuomilehto et al 2001 , Knowler et al 2002).***

The American Diabetes Association recognizes the PCOS as a risk factor that justifies screening for type 2 diabetes, ***(American Diabetes Association 2004).***

On the other hand, it may be argued that since only a subgroup of women with the polycystic ovary syndrome go on to have glucose intolerance, just that high-risk subgroup should be screened. Factors that augment the risk are increased body weight (particularly if body fat is distributed in an android pattern), a history of gestational diabetes, type 2 diabetes in a first-degree relative, and Caribbean-Hispanic, Mexican-American, ***(Dunaif et al 1993).***

Integral to this issue is whether the measurement of fasting glucose, with or without simultaneous measurement of fasting insulin, is sufficient

to assess the risk of glucose intolerance. Although a supranormal fasting glucose concentration increases the likelihood that a patient will have an abnormally elevated glucose concentration at two hours during a formal oral glucose-tolerance test, a normal fasting glucose concentration does not necessarily predict normal glucose tolerance and is insufficient to distinguish between women who have normal glucose tolerance and those who have impaired glucose tolerance. Thus, if the goal is to detect impaired glucose tolerance for the purpose of intervening to reduce the risk of conversion from impaired glucose tolerance to type 2 diabetes, an oral glucose-tolerance test should be performed, ***(Knowler et al 2002)..***

Although insulin resistance is virtually inherent in the phenotype of the PCOS, there is little to support its formal assessment outside the context of a clinical study. First, insulin resistance is not a diagnostic criterion, nor is it recommended as a factor to be used in determining treatment in the PCOS. These recommendations relate to the observation that the clinical response to insulin-lowering therapies does not appear to be related to the magnitude of insulin resistance. Insulin resistance is virtually universal and maximal once the body-mass index (the weight in kilograms divided by the square of the height in meters) exceeds 30; thus, there appears to be little value gained by formal measurement of insulin sensitivity in obese patients. Finally, it is important to note that the simple and readily available methods proposed as tests to quantify insulin resistance — the ratio of fasting glucose to insulin, ***(Legro et al 1998),*** or the homeostatic model assessment index, ***(Legro et al 2004)*** — may be misleading, since both have been shown to lack precision when compared with the gold-standard method for quantifying whole-body insulin resistance (i.e., the hyperinsulinemic–euglycemic clamp), ***(Diamanti et al 2004).***

Pathophysiology of Hyperinsulinemia & Insulin Resistance

Insulin and insulin receptor

Insulin is a polypeptide hormone secreted by the β-cells of the pancreas. It plays a dominant role in the regulation of glucose homeostasis. Its classic target tissues include the liver, muscle and fat. Insulin suppresses hepatic glucose output, inhibits glycogenolysis and gluconeogenesis, and promotes glycogen synthesis. It stimulates peripheral glucose uptake in muscle and fat, induces protein synthesis, cell growth and differentiation, and inhibits lipolysis ***(Yen et al. 1999).***

The insulin receptor *(Fig 3)* is a transmembrane glycoprotein containing two α & β - dimers connected by disulfide bonds. The extracellular α subunits contain the insulin binding sites and the intracellular components of the membrane-spanning β–subunits contain intrinsic protein tyrosine kinase activity. The first step in glucose uptake by the muscle cell is initiated by the binding of insulin to the α - subunit of the insulin receptor, that leads to stimulation of the tyrosine kinase activity in the β - subunit, initiating a cascade of intracellular protein phosphorylation *(Fig. 3)* ***(Yen et al. 1999).***

The tyrosine-phosphorylated insulin receptor tyrosinephosphorylates insulin receptor substrates (IRS), which bind signaling molecules, such as specific domain of the phosphatidylinositol 3-kinase (PI -3 kinase) ***(White 1998),*** a necessary step for the initiation of glucose transport ***(Dunaif 1999, Poretsky et al. 1999).*** In addition,

mitogen-activated protein kinase (MAPK) is also phosphorylated after insulin receptor binding, thus inducing the growth-promoting effects of insulin *(Fig 3)* ***(Poretsky et al. 1999)***.

An alternative signalling pathway has been described, involving generation of inositolglycan second messengers at the cell membrane independently of β-subunit tyrosine kinase activation. This alternative pathway may mediate stimulation of ovarian steroidogenesis, explaining why the stimulation of ovarian steroidogenesis by insulin is still operative despite of insulin resistance *(Fig 3)* ***(Nestler et al. 1998a)***.

The mechanisms by which the insulin signal is terminated remain incompletely understood. Receptor mediated endocytosis and recycling may be important to signal termination ***(White 1998).*** The mechanisms implying insulin receptor function in insulin resistance in cases with PCOS are discussed more in detail below.

Figure---------3----------

Mechanism Of Insulin secretion

In the presence of insulin resistance, pancreatic β-cell secretion increases and type 2 DM develops when the compensatory increase in insulin levels is no longer sufficient to maintain euglycaemia. Fasting

hyperinsulinaemia is present in obese PCOS women, and the insulin response to an oral glucose load is increased in both obese and non-obese PCOS women ***(Dunaif & Finegood 1996).***

Studies concerning the acute insulin response to an intravenous glucose load (first-phase insulin secretion) have shown controversial results in PCOS. First-phase insulin secretion has been shown to be similar to that in weight-matched control women ***(Dunaif & Finegood 1996),*** but, when related to the degree of insulin resistance, it was decreased below the level in weightmatched control women, in cases of both PCOS and obesity ***(Ehrmann et al. 1995, Dunaif & Finegood 1996).*** This was more pronounced in PCOS women with a first-degree relative with type 2 DM, suggesting that these women may be at a particular risk of developing glucose intolerance ***(Ehrmann et al. 1995).*** On the other hand, the results of some studies suggest that there is increased first-phase insulin secretion in PCOS women independent of body mass index (BMI) and body fat distribution ***(Holte et al. 1994a, Holte et al. 1995).***

Mechanism Of Insulin clearance

A decrease of insulin clearance can result in hyperinsulinaemia in PCOS. Hepatic insulin extraction in subjects with PCOS has been shown to be either decreased ***(Buffington & Kitabchi 1994),*** normal ***(Peiris et al. 1989),*** or heterogeneous, despite a similar degree of insulin sensitivity (***Ciampelli et al. 1997).***

The decline in hepatic insulin extraction could be associated with an increase of abdominal body fat and mediated in part by increased

androgen activity. Because of the increased lipolysis characteristic of adipocytes localised in abdominal fat, androgens may predispose women with PCOS to increased hepatic exposure to free fatty acids (FFAs), which, in turn, could decrease hepatic insulin binding, insulin degradation and hepatic insulin clearance ***(Buffington & Kitabchi 1994, Wiesenthal et al. 1999).***

Mechanism of insulin resistance & hyperinsulinemia in PCOS women:

Mutations in the insulin receptor gene (Type A syndrome of insulin resistance , or the presence of autoantibodies against the insulin receptor (Type B syndrome) were observed in these syndromes ***(Dunaif 1997).***

Burghen et al. (1980), reported that women with PCOS had basal and glucose-stimulated hyperinsulinaemia, suggesting the presence of insulin resistance. Moreover, they showed a significant positive correlation between insulin and androgen levels, and suggested an aetiological relationship between these two features. Women with PCOS have a greater frequency and degree of both hyperinsulinaemia ***(Dunaif et al. 1987)*** and insulin resistance ***(Robinson et al. 1992)*** than weight-matched controls.

The nature of the complex interrelationship of insulin resistance, hyperandrogenism and the distribution of body fat remain controversial ***(Holte et al. 1994a, Holte et al. 1995, Holte 1996, Dunaif 1997, Dunaif 1999).***

Studies on isolated cultured fibroblasts have shown that in approximately 50% of fibroblasts from women with PCOS there is increased basal receptor serine phosphorylation ***(Dunaif et al. 1995).***

As insulin receptor serine phosphorylation has been shown to decrease its tyrosine kinase activity *(Fig 4)* ***(Dunaif et al. 1995, Dunaif 1997, White 1998),*** this mechanism could be important in the pathogenesis of insulin resistance in PCOS ***(Dunaif et al. 1995).***

It is possible that serine phosphorylate insulin receptor, causes insulin resistance, and also serinephosphorylate P450c17 α increasing the 17,20 lyase activity of this enzyme and causing hyperandrogenism, thus explaining the association between PCOS and insulin resistance ***(Dunaif 1997).***

Further studies have suggested that the factor responsible for the excessive serine phosphorylation could be genetically programmed ***(Dunaif et al. 1995, Dunaif 1999).***

These findings are in accordance with recent twin and family studies where insulin resistance seemed to be a genetic defect in PCOS ***(Legro et al. 1998).***

The molecular mechanism of insulin resistance in PCOS is not known, but appears to be different from that found in other syndromes of insulin resistance e.g. leprechaunism (which is a rare syndrome in young girls with a mutation in the insulin receptor gene and associated with severe insulin resistance), an abnormality of insulin receptor phosphorylation in 50% of women with PCOS have been reported, ***(Dunaif et al., 1995)***.

It is suggested that perhaps another 30% may have a defect in post receptor signal transduction between the receptor kinase and the . glucose transport system ***(Dunaif et al., 1993).***

Studies of insulin action in isolated PCOS adipocytes have revealed marked decrease in insulin sensitivity together with significant decrease in glucose transport. In contrast to NIDDM such defects in PCOS occur in the absence of obesity, glucose intolerance, or changes in body fat topography. Moreover, these abnormalities don't correlate significantly with sex hormone levels, suggesting that abnormalities of insulin action in PCOS may be intrinsic ***(Dunaif et al., 1993).***

Further evidence indicating that decreased insulin sensitivity is an intrinsic defect is provided by studies of PCOS insulin receptors isolated from cultured skin fibroblasts. Receptors from some PCOS women with insulin sensitivity have absent insulin-stimulated receptor (tyrosine) autophosphorylation, whereas insulin-independent serine phosphorylation of the receptor is increased. Other PCOS women have normal receptor autophosphorylation ***(Dunaif et al., 1995)***.

Indeed their appears to be a bimodal distribution of insulin receptor autophosphorylation of PCOS, approximately 40% of affected women have a marked decrease and about 30% have completely normal insulin-stimulated receptor autophosphorylation, ***(Dunaif et al., 1995).***

Studies show that decreased insulin responsiveness in PCOS adipocytes is secondary to decreased levels of Glucose transporter proteins (GLUTp), this defect is also independent of obesity, glucose

intolerance and sex hormone. Because the GLUTp is not expressed in fibroblasts, it is not possible to tell whether changes in GLUTp abundance in PCOS are an intrinsic defect or secondary to the already identified abnormalities in insulin receptor signal transduction ***(Rosenhaum et al., 1993).***

Therefore, several alterations in different steps of insulin action may be the causes of hyperinsulinemia in patients with PCOS. The defects are probably heterogenous. In turn, excess circulating insulin influence the clinical presentation of PCOS in several major ways:

1. Directly increasing ovarian androgen secretion.

2. Reducing IGF-BPI production and as a consequence increasing bioavailable IGF-BPI activity.

3. Elevation of insulin and bioavailable IGF-BPI influencing gonadotrophin secretion, adrenal androgen secretion and also contributing to abnormalities in lipid and lipoproteins ***(Lobo et al., 1996)***.

Additionally, androgen production may be enhanced by an increase in the biological activity of IGF-I/II as insulin is shown to reduce concentrations of IGF binding protein IGF-BPI ***(Rosenfeld & Barnes et al., 1990).***

The main characteristic of insulin sensitivity in PCOS is that it is only partial resistance which involves metabolic activities of insulin ***(Conway et al., 1993)*** but does not prevent insulin effect on its receptors

on the ovary or the effect of insulin on SHBG and IGF-BPI produced by liver cells ***(Carmina et al., 1995).***

It has been suggested that the main effect of insulin on the ovary is not the direct activation of androgen , secretion but the derangement of the regulation of androgen synthesis preventing the down regulation of LH receptors and stimulating the activity of the P450,C17 coenzyme ***(Ehrmann & Sturis et al., 1995).***

This results in the increase of androgen and insulin secretion, which coupled with the effect of insulin in reducing SHBG produces the hyperestrogenism and gonadotrophin abnormalities that perpetuate the syndrome. PCOS is thought to be present around the time of pubrty because of the concurrent effect of the pubertal activation of ovarian function and the pubertal decrease of insulin sensitivity and increase of IGF-I hepatic production ***(Savage et al., 1992)***.

Nader (1991) proposed the following model providing a unified concept of the androgen-insulin connection in PCOS. Hyperinsulinemia, regardless of its cause and in the presence of permissive concentrations of gonadotrophins, stimulates the ovarian thecal stromal compartments to produce androgens. These androgens produce two actions: a direct impairment of hepatic and peripheral insulin action and an indirect action through increasing the size and recruitment of abdominal adipocytes. These lead to the development of android obesity and through their specific metabolic qualities lead to a further insulin resistance state and hyperinsulinemia that is independent on the degree of overweight (i.e. via the high free fatty acid milieu suggested by ***(Kissebach and Peiris, 1989).***

This model by ***Nader (1991),*** explains everything known about PCOS and its androgen insulin connection. It explains how states of insulin resistance and hyperinsulinemia of diverse causes can be associated with hyperandrogenism. It explains how lowering gonadotrophins (e.g. with the use of gonadotrophin-releasing hormone analogues) may lower androgens without altering insulin resistance. It explains the common association between PCOS and android obesity and finally it explains how, under some circumstances, lowering androgen levels may indeed improve insulin sensitivity.

Role of Adenosine regulation of Insulin sensitivity *in PCOS*

The characteristics of insulin resistance in adipocytes from PCOS subjects, *i.e.* normal insulin binding, normal glucose transport activity and responsiveness, and impaired sensitivities for antilipolysis and

glucose transport stimulation, are very similar to the conditions created in rat adipocytes by depletion of cellular adenosine' ***(Ciaraldi TP. 1988).***

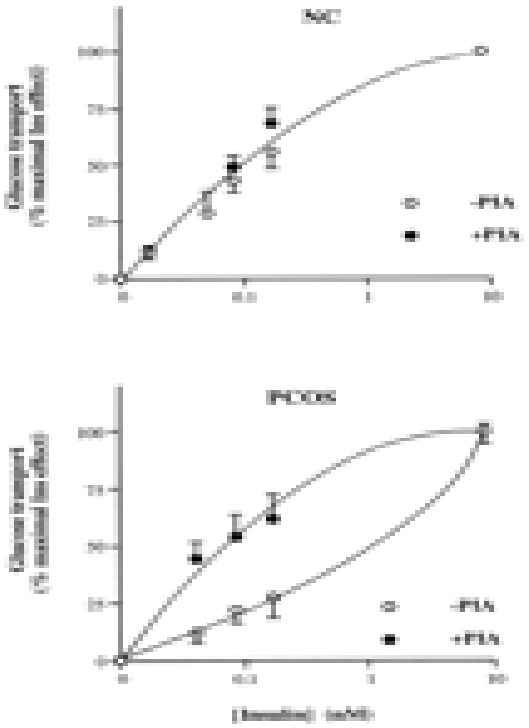


Figure 4. Influence of adenosine replacement on glucose transport in adipocytes from NC and PCOS subjects. Insulin dose-response curves for glucose transport stimulation in control and PIA-treated cells from NC (*top panel*) and PCOS (*lower panel*) subjects. Results were normalized against the maximal insulin effect (with or without PIA) for each individual and are the average ± SEM (n = 5 for NC; n = 7 for PCOS).

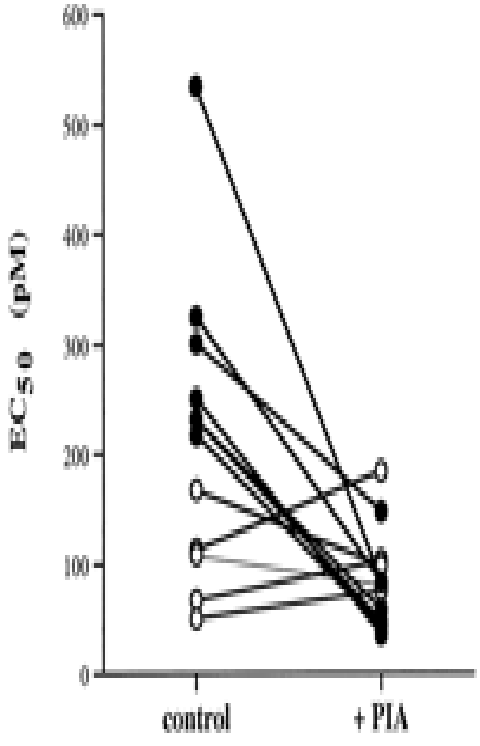


Figure 5. Effect of adenosine replacement on insulin sensitivity in adipocytes from NC (○) and PCOS (•) subjects. EC_{50} values were determined from dose-response curves for glucose transport stimulation in control and PIA-treated (2 µmol/L) cells. Each *line* connects values from a single individual.

Insulin resistance is now recognized as a common feature in women with PCOS ***(Dunaif 1995).*** However, the mechanisms underlying this insulin-resistant state are poorly understood. Although insulin resistance is a nearly universal finding in obese PCOS subjects ***(Dunaif 1995),*** there is less unanimity about the presence of insulin resistance in *nonobese PCOS subjects* ***(Holte 1994).***

Adipocytes from the current PCOS subjects displayed normal maximal antilipolytic responsiveness to insulin. This is similar to the situation for glucose transport, where insulin responsiveness was also normal. Interestingly, in PCOS cells, the sensitivity to insulin's antilipolytic effects was significantly reduced. The 3-fold difference in EC_{50} values for this response between NC and PCOS cells was the same as that for glucose transport stimulation. This suggests that the site of impaired insulin action in PCOS occurs before divergence of the glucose transport stimulation and antilipolytic pathways, and that the final effector systems responsible for antilipolysis are intact in PCOS, ***(Yki-Jarvinen et al. 1987).***

Depletion of cellular adenosine in rat adipocytes creates a condition with normal insulin binding, normal glucose transport activity, and impaired insulin sensitivity for glucose transport stimulation **(*Ciaraldi et al 1988)*** that resembles the behavior in PCOS adipocytes. Similar observations have recently been made in human adipocytes ***(Heseltine et al 1995).***

Insulin sensitivity in adenosine-depleted rat adipocytes can be restored by treatment with a nonmetabolized adenosine analog, PIA ***(Ciaraldi et al 1988)***

We performed a similar manipulation in PCOS adipocytes and showed that PIA addition causes a leftward shift of the dose-response curve for glucose transport stimulation. As such, this effect leads to normalization of insulin sensitivity in these cells. In contrast, adenosine was without effect on the shape of the glucose transport dose-response curve in NC cells, (***Ciaraldi et al 1988).***

Studies in rat , and human adipocytes have shown that insulin sensitivity for antilipolysis is also impaired by adenosine depletion. This would suggest that the adenosine-dependent event(s) in insulin signaling occur before the pathways for glucose transport and antilipolysis diverge, just as is the case for impaired insulin sensitivity in PCOS adipocytes. From these results it is reasonable to anticipate that PIA treatment of PCOS adipocytes would also normalize insulin sensitivity for antilipolysis. Unfortunately, due to the limited amount of tissue available from each biopsy we were unable to test this hypothesis directly ***(Green et al 1992 , Heseltine et al 1995).***

Adenosine acts through a cell surface A_1 receptor to help maintain a normal state of insulin sensitivity for glucose transport ***(Ciaraldi et al 1988, Green et al 1992 ,).***

Although the specific steps in the insulin signal transduction cascade that are influenced by adenosine are unknown, the effect appears to involve the efficiency of the coupling mechanisms between the insulin receptor and the glucose transport system. The current results suggest that the mechanism of decreased insulin sensitivity in PCOS cells involves an adenosine-sensitive step, and this could involve alterations in adenosine production and release, expression of specific A_1 adenosine receptor subtypes, or the efficiency of A_1 receptors coupling through distinct G

proteins to pathways that modulate insulin sensitivity. These possibilities are currently under investigation. Evidence in the current report argues against adenosine depletion or the presence of a generalized impairment of adenosine action as the cause of the insulin resistance. Endogenous adenosine maintains a tonic inhibition of adipocyte lipolysis ***(Ohisalo et al 1984).***

Removal of adenosine results in stimulation of basal lipolysis, often up to levels at which there is no further stimulation by lipolytic agents ***(Ohisalo 1981).***

The normal basal and isoproterenol-stimulated rates of lipolysis in PCOS adipocytes indicate that the perturbation of adenosine signaling in PCOS may be specific for control of insulin sensitivity. There are several physiological conditions under which adenosine sensitivity of adipocytes is regulated. These include lactation ***(Vernon et al 1983)*** and chemically induced hypothyroidism ***(Ohisalo et al 1979),*** where cells are more sensitive to adenosine. Massively obese humans display a reduced sensitivity to the antilipolytic effects of adenosine ***(Ohisalo et al. 1992)*** that is improved after weight ***loss (Koopmans et al 1989).***

Any alterations in insulin sensitivity in those conditions could be accounted for by changes in insulin binding. Impaired insulin sensitivity in adipocytes from obese and noninsulin-dependent diabetes mellitus subjects was also found to be due to decreases in insulin binding ***(Olefsky et al 1985).***

The obese NC subjects studied in the current report could also be considered insulin resistant compared to lean individuals. Yet, their insulin sensitivity was not influenced by added PIA, suggesting that

alterations in adenosine modulation of insulin action are not common to all insulin-resistant states. However, we are unaware of any systematic evaluation of this question, and further studies are necessary to establish whether this particular defect is indeed selective to PCOS.

The identity of the insulin signaling event(s) that is perturbed in PCOS is also an open question. Dunaif, have reported on increased serine phosphorylation of insulin receptors isolated from cultured fibroblasts in a subset of PCOS subjects ***(Dunaif et al 1995).***

Insulin-stimulated receptor tyrosine kinase activity was also decreased in these subjects. The potential importance of such a difference in receptor kinase activity in fibroblasts is uncertain, because these workers failed to find any correlations between receptor phosphorylation and either *in vivo* or *in vitro* insulin action ***(Dunaif et al 1995).***

Investigations of cultured fibroblasts obtained from many of the same subjects whose adipocytes were studied in the current report suggested that insulin action was, in fact, normal in fibroblasts ***(Ciaraldi et al 1995.*** In addition, in earlier studies indicated that insulin receptor kinase activity from PCOS adipocytes displayed little or no difference compared to NC adipocytes ***(Ciaraldi et al 1995).***

Considerable additional work will be necessary to identify the crucial steps. Signaling events downstream of the receptor kinase are currently being investigated as potential sites of the impaired insulin sensitivity of PCOS. Evidence exists suggesting that PCOS can be an inherited disease ***(Legro 1995),*** and therefore, the form of insulin resistance present in these patients may also be genetic. It is possible that the adenosine-sensitive step in PCOS cells represents the site of a genetic

abnormality in these patients, and further dissection of the insulin signaling pathways in PCOS may lead to important new insights into the pathogenesis of this common syndrome as well as better understanding of the basic mechanisms of insulin action ***(Legro 1995).***

Actions of insulin and insulin like growth factors on oocyte maturation

Insulin appears to be important in oocyte maturation ***(Pellica et al., 1987)***.

Insulin has been found in follicular fluid of some but not all patients. Whether it was secreted or sequestrated has not been demonstrated. It was found to correlate with follicular fluid progesterone levels but not with estradiol or androstenedione ***(Diamond ct al., 1985)***.

Also recent evidence suggests that insulin, IGF I and IGF II might be important regulators of thecal and stromal androgen production. This action might be mediated through the following;

3. Inducing functional activities of P 450.

4. Augmenting the ability of LH to induce P 450 and 17-hydroxylase /C 17-20 lyase activities in the theca interstitial cells ***(Barbieri & Markis et al., 1983)***.

Some of these effects of insulin may be indirect and mediated by the decrease of hepatic secretion of IGF-BPI with an increase in the activity of circulating IGF-1 on the ovary leading to stimulation of androgen secretion ***(Bregen et al., 1993)***, increase the binding of LH to

its ovarian receptors ***(Cara et al., 1988)*** and activate the coenzyme P450,C17.

Moreover, IGF-I may be responsible for some of the morphologic alterations of PCOS, altering the balance between follicular growth and follicular atresia ***(Carmina et al., 1996)***.

Also according to ***Diamond 1985 ,*** follicular fluid insulin and progesterone are positively correlated and that the enhanced pituitary hypothalamic LH secretion induces a switch in the thecal cell function from an androgen to a progesterone secreting tissue. High levels of progesterone are shown to have an inhibiting effect on oocyte maturation and this whole process also leads to a reduced follicular estrogen and ultimately follicular atresia, (***Diamond et al., 1985)***,.

The Insulin like Growth Factor – Insulin like Growth Factor Binding Protien system

Insulin-like growth factors (IGF-I and IGF-II) are single-chain polypeptides synthesized mainly in the liver. They interact with specific cell membrane receptors to stimulate cellular mitosis and differentiation. They can act via autocrine, paracrine and endocrine mechanisms ***(Sara & Hall 1990).***

Both IGF-I and IGF-II circulate in plasma tightly bound to specific binding proteins (IGFBPs), which regulate the physiological actions of the IGFs by inhibition or stimulation, depending on the type of binding protein and the target cells ***(Drop 1991).***

Insulin-like growth factors stimulate granulosa cell proliferation and aromatase *in vitro*. Insulin-like growth factor-II is the major IGF in human ovary, expressed primarily in granulosa cells of antral and preovulatory follicles and in theca cells ***(Voutilainen et al. 1996).***

Gonadotrophins are major regulators of the ovarian IGF family. The insulin and type I IGF receptors are similar, whereas the type II IGF receptor consists of a long extracellular domain and a short cytoplasmic domain. The type I IGF receptor binds insulin with low affinity and can be activated by insulin ***(Yen et al. 1999).***

Insulin receptors and type I and II IGF receptors are abundant in the ovaries. Hyperinsulinaemia up-regulates the number of type I IGF receptors ***(Ehrmann 1999).***

The actions of IGF in the ovary include augmentation of DNA synthesis and steroidogenesis ***(Poretsky et al. 1999).***

Thus, hyperinsulinaemia could contribute to raised androgen concentrations in PCOS through ovarian stimulation ***(Holte 1996),*** either directly through the insulin receptor, through "spill-over" on type I IGF receptors, or through a hybrid insulin/type I IGF receptor in the ovarian stroma, synergising with LH, promoting hyperandrogenism and follicular atresia ***(Giudice 1992).***

On the other hand, a recent study suggests that insulin stimulation of T production in the ovary is mainly mediated by the insulin receptor ***(Nestler et al. 1998a).***

The biologically available circulating IGF-I may also be enhanced through reduced concentrations of IGFBP-1 in obese women with PCOS

as a result of elevated circulating insulin levels, thus stimulating ovarian androgen secretion and further worsening insulin resistance and hyperinsulinaemia *(Fig.10)* ***(Laatikainen et al. 1990).***

Additionally, local dysregulation in the IGFBP/IGF system may inhibit IGF or FSH action in the PCOS follicle, impairing follicular development and dominant follicle selection ***(Voutilainen et al. 1996, Giudice 1999).***

Effects of insulin and insulin like growth factors on ovarian steroidogenesis:

A summary of the effects of hyperinsulinaemia on ovarian function is presented in "Table 1"

Table 1. **Effects of insulin on ovarian function (*modified from Poretsky et al. 1999):***

Effect	Organ
Directly stimulates steroidogenesis	ovary
Stimulates 17β-hydroxylase	ovary
Stimulates or inhibits aromatase	ovary
Up-regulates LH receptors	ovary
Promotes ovarian growth and cyst formation synergistically with LH/hCG	ovary
Down-regulates insulin receptors	ovary
Up-regulates type I IGF receptors or hybrid insulin/type I IGF receptors	ovary
Inhibits IGFPB-1 production	ovary, liver

Although insulin has been shown to stimulate gonadotrophin release in isolated rat pituitary cells ***(Adashi et al. 1981),*** studies on insulin action on gonadotrophin release in humans have yielded conflicting results. Insulin may act on the pituitary, increasing its sensitivity to GnRH. Alternatively, it may potentiate the steroidogenic ovarian response to gonadotrophins by increasing the LH receptor number. Decreases in LH levels have been observed after insulin-lowering therapies ***(Velazquez et al. 1994).*** However, 10-day suppression of insulin levels in 5 PCOS subjects with diazoxide, resulting in decreases in serum T levels, did not alter circulating LH levels ***(Nestler et al. 1989).***

Thus, it is possible that insulin-mediated changes in gonadotrophin release contribute to the changes in steroidogenesis produced by insulin ***(Anttila et al. 1993, Dunaif 1997).***

Recent investigations as those of ***Baranao and Hammond (1984),*** suggested that many other proteins may play major roles in ovarian folliculogenesis and steroidogenesis. The emerging consensus is that insulin and insulin like growth factors exert important effects on ovarian functions. Insulin belongs to a group of growth factors with similar biochemical characteristics. The family of IGFs includes insulin, IGF-I (somatomedin C), IGF-II (somatomedin A), nerve growth factor and relaxin (***Baranao and Hammond 1984)***.

At high concentrations, many of these hormones cross reacted with receptor sites specific for other hormones of the family. For example, high concentrations of insulin can displace IGF I from fibroblast I receptors. In porcine ovarian granulosa cells, it has been reported that

insulin may stimulate progesterone production by interacting with IGF I receptors ***(Baranao and Hammond, 1984).***

The sequence of events in hyperinsulinemic hyperandrogenism

Androgens may produce mild insulin resistance, by increasing the number of less insulin sensitive type II b skeletal muscle fibres ***(Holmang et al. 1992)*** and by inhibiting muscle glycogen synthase activity ***(Rincon et al. 1996)***

However, androgen administration does not result in insulin resistance of the same magnitude as that seen in PCOS ***(Polderman et al. 1994).*** Furthermore, decreasing androgen levels by way of GnRH agonists ***(Dunaif et al. 1990)*** or antiandrogens ***(Moghetti et al. 1996b)*** does not completely restore normal insulin sensitivity.

**** There are several studies which indicate that hyperinsulinemia produces hyperandrogensim and not the reverse :**

- The administration of insulin to women with PCOS increase circulating androgen levels ***(Elkind-hirsch et al., 1991).***
- The administration of glucose to hyperandrogenic women increase the circulating levels of both insulin and androgens ***(Smith et al., 1987).***

- Weight loss decreases the levels of both insulin and androgens ***(Kiddy et al., 1989)***.

- In vitro, insulin stimulates thecal cell androgen production ***(Barbieri et al., 1986)***.

- The experimental reduction of insulin levels (using dioxide) in women with PCOS reduces androgen levels ***(Nestler et a; 1989)***, *while (**Prelevic et al; 1990)***, employed an analogue of somatostatin.

- ***(Dunaif and Graf; 1989)*** demonstrated that these acute rises in androgen levels following glucose stimulated insulin release in women with PCOS are independent of any change in LH secretion.

- After normalization of androgens with GnRH agonist treatment, the insulin response lo glucose testing remains abnormal in obese women with PCOS ***(Dale et al; 1992).***

The clinical presentation of patients with insulin resistance (whether they have impaired glucose tolerance or diabetes mellitus) depends on the ability of the pancreases to compensate for the target tissue resistance to insulin. This compensatory response of hyperinsulinemia leads to hypertension. Resistance to insulin is further associated with increased triglycerides and decreased HDL cholesterol levels ***(Haffner et al;, 1992)***.

The Role Of Obesity in Insulin Sensitivity & PCOS

At least 50% of women with PCOS are obese ***(Franks 1995).*** Obesity and PCOS have a synergistic negative impact on insulin sensitivity ***(Dunaif et al. 1989, Morales et al. 1996).***

Furthermore, hyperandrogenicity in women is associated with an increase of abdominal fat, which has a high lipolytic activity, releasing FFAs into the blood circulation ***(Bouchard et a; 1993).***

Free fatty acids compete with glucose for uptake in muscle and fat cells, resulting in increased FFA oxidation and impaired insulin-mediated glucose utilisation (glucose oxidation and glycogen deposition) in skeletal muscle and in an acceleration of gluconeogenesis in the liver, ***(DeFronzo; et al 1992).***

All these metabolic features interfere with hepatic and peripheral insulin action on glucose metabolism ***(Ferrannini et al. 1983)*** and thereby induce or worsen insulin sensitivity, ***(Dunaif et al. 1992, Holte et al. 1995, Holte 1996).***

In addition, abdominal obesity is associated with high oestrogen production, increased serum oestrone concentrations, and greater amounts of free E2 as a result of decreased SHBG concentrations, favouring a hyperoestrogenic state ***(Pasquali et al. 1994).***

This exerts positive feedback regulation upon LH release, further increasing ovarian androgen secretion ***(Pasquali et al. 1997).***

Obesity, as well as PCOS, is also characterized by increased activity of the opioid system, which in turn may stimulate insulin secretion, (***Pasquali et al. 1997).***

Finally, diet may play some role in the development of PCOS. There are data suggesting that women eating vegetarian and fibre-rich diets have lower androgen concentrations than those having typical Western diets ***(Hill et al. 1980).*** Furthermore, high lipid intake is correlated with low SHBG concentrations (***Wild et al. 1985).***

Thus, both low fibre and high lipid diets may to some degree favour the development of hyperandrogenism and PCOS in susceptible individuals,***(Pasquali et al. 1997).***

Overweight anovulatory PCOS women with hyperandrogenism have a characteristic distribution of body fat known as android obesity. Android obesity is the result of fat deposited in the abdominal wall and visceral mesenteric region. This fat is more sensitive to catecholamines, less sensitive to insulin and more active metabolically. This fat distribution is associated with hyperinsulinemia, impaired glucose tolerance, diabetes mellitus and an increased androgen production rates ***(Pasquali et al., 1993).***

Hyperinsulinemia and hyperandrogenism, however are not confined to anovulatory women who are overweight, it is important to note that the combination of increased androgen secretion and insulin resistance has been reported in both obese and non obese anovulatory

women ***(Morales ct al., 1996).*** For this reason, some have suggested that hyperandrogenic women with polycystic ovaries could be divided into two groups: those with obesity, insulin resistance, hyperinsulinemia and normally or minimally elevated LH levels and those with elevated LH levels have no insulin resistance and normal insulin levels ***(Dale et al., 1992).***

Hyperinsulinemia and hyperandrogenism are not explained, therefore solely by obesity and specifically android obesity. However the presence of obesity adds the insulin resistance and hyperinsulinemia associated with obesity to that which is specifically unique to the anovulatory polycystic ovary state ***(Jahanfar et al., 1995).***

In obese insulin resistant women, caloric restriction that results in weight reduction will reduce the severity of insulin resistance (a 40% decrease in insulin level with a 10 kg weight loss), this decrease in insulin levels would result in marked decrease in androgen production (a 35% decrease in testosterone level with a 10 kg weight loss ***(Kiddy et al., 1992)***

Clinical Presentation of Polycystic Ovary Syndrome (PCOS)

Stein and Leventhal in 1935 described a "syndrome"' consisting of a rigid criteria which included absent or infrequent menstrual cycles, hirsutism, obesity and enlarged cystic ovaries.

Later a broad spectrum of clinical presentation came to be recognized and it is now clear that many women have polycystic ovaries in the absence of one or two of the triad of hirsutism, obesity and anovulation ***(Goldzieher, 1981)***.

It seems that the syndrome stein and leventhal identified characterizes only a small fraction of a much larger population of patients with polycystic ovaries ***(Goldzieher and Dizerega, 1985).***

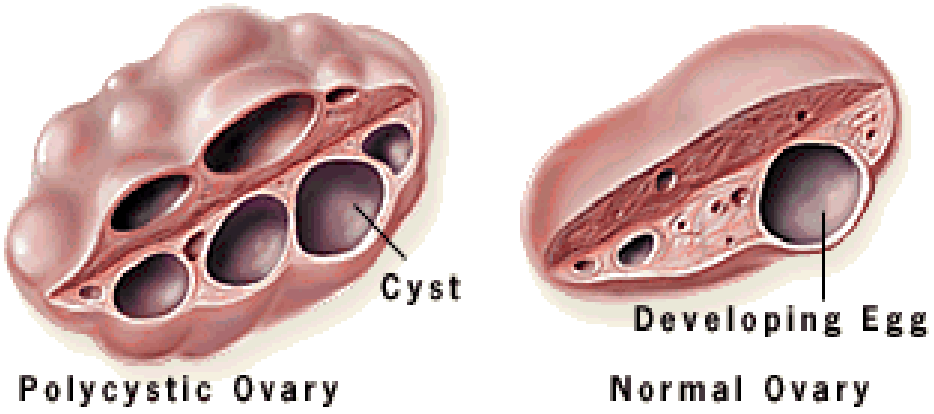
It is now clear that the presence of polycystic ovaries can be associated with a variety of clinical and biochemical features, ranging from the typical stein-leventhal picture at one end of the spectrum to normal ovulatory cycles occurring in non-hirsute women at the oilier ***(Yen, 1980)***.

It is now apparent that obesity is not essential and that while hirsutism is customary, it is by no means universal. The enlarged ovaries may be difficult to feel on examination, even under anaesthesia, and additional help by laparoscopy is frequently needed, occasionally, the ovaries although polycystic, may not be enlarged. The macroscopic appearance is typical, but microscopic examination of the ovarian tissue

reveals no unique features. Whether the ovaries are enlarged or not, the- presence of multiple sub cortical follicular cysts and thickened ovarian capsule with increased ovarian stroma echogenicity, define the ovaries as polycystic ***(Pache et al.,1993)***.

Figure "6" ***Macroscopic Picture Of PCO:***

The multiple cysts in a polycystic ovary are follicles that have matured but, due to abnormal hormone levels, were never released. In a normal ovary, a single egg develops and is released each month.



Clinically, PCOS appears with variable symptoms, the most commonly noticed are infertility, hirsutism, amenorrhea, menstrual irregularities and obesity. Of a total of 1079 case, 187 cases documented to have polycystic ovaries , 74 percent presented with infertility, 79 percent with hirsutism, 51 percent with amenorrhea, 41 percent with obesity and 29 percent with dysfunctional uterine bleeding.

It is evident that some women with PCOS, proven surgically, histologically or on ultrasound, have ovulatory menstrual cycle ***(Adams et***

al, 1985). Therefore women may have PCOS without clinical symptoms or signs. On the other hand, failure of ovulation in PCOD may present as amenorrhea or irregular menstrual bleeding ***(Yen, 1980)***.

** Incidence of PCOS:

Most of diagnosed cases of PCOS depends largely on suspicion and on the little diagnostic criteria of individual clinician and so there is little idea about the true incidence of PCOS, same frequency of diagnosis depends on the index of suspicion, the prevalence of PCOS in community population based on basis of clinical and endocrinological data found to be 21% ***(Farqnhar et al., 1994)***.

** Age:

The great majority of the PCOS patients were first seen between the age 20 and 30 years, presumably due to the gradual appearance of the clinical manifestations of PCOS in the post pubertal reproductive years ***(Jeffcoate, 1980).***

Clinical symptoms:

(1) Hirsutism:

Hirsutism is a distressing presenting symptom in patients seen in the reproductive endocrinology and infertility clinic. It is the result of androgen action on the skin. This may be due to excessive production by the adrenals or by the ovaries or increased skin sensitivity to these androgens. The major cause of hirsutism in polycystic ovarian disease is ovarian androgens ***(Franks et al., 1985)***.

When hirsutism presents with oligoinenorrhea, amenorrhea and or infertility, the most likely diagnosis is the PCOS, ***(White and Turner, 1994)***.

PCOS is a spectrum of disease from idiopathic hirsutism with regular cycles to the polycystic ovarian syndrome with oligomenorrhea or amenorrhea. In both cases, patients have morphological polycystic ovaries on ultrasound and evidence of hyperandrogenemia which mediates the hirsutism. This androgen excess is derived from the ovaries or the adrenals in PCOS patients, but there is also increased evidence of enhanced 5α-reductase activity in these patients ***(Lobo et al., 1987)***.

The hirsutism is considered to be the most sensitive marker for increased androgen production, followed by ance, increased oiliness of the skin and menstrual irregularity ***(Speroff et al., 1994a).***

Severe hirsutism may be associated with slight elevation of androgen, while substantial elevation of androgens may not always result in hirsutism ***(Lobo, 1991)***.

The apparent dissociation between androgen levels and hirsutism does not mean that a causal relationship does not exist. Hirsutism may have been induced by previous androgen excess and androgen levels at the time of sampling may be normal. Conversely, the finding of high androgen in the absence of hirsutism may result from episodic secretion of androgens **(*Yen, 1991)***.

Hirsutism involves principally the sexual hair or hair which responds to sex steroids. Sexual hair grows on the face, lower abdomen, interior thighs, the chest, the breasts, the pubic area, and in the axillae.

Once androgen influences hair follicles in sexual areas, larger, longer and more pigmented hair is induced. So, androgen stimulates sexual hair follicle conversion from villus to terminal hair growth pattern, but once established these patterns persist despite withdrawal of androgen for its remaining life cycle, and this explains the difficulty in treating hirsutism once the hair follicle is stimulated ***(Speroff et al., 1994)***.

Pasupuleti and Horton, (1992), suggested that hair growth is influenced significantly by insulin like growth factor 1 (IGF-1) and that IGF-1 stimulates 5-α reducate activity. Approximately two thirds of all patients diagnosed with PCOS were insulin resistant. Although serum IGF-1 levels usually are normal in PCOS patients, levels of circulating IGF-1 binding protein are decreased in PCOS. Thus level of IGF-1, not specifically bound, may be elevated and enhance 5-α reductase activity in PCOS.

So, there is increased IGF-1 activity in PCOS patients with insulin resistance and hyperandrogenic patients ***(Speroff et al., 1994)***.

It has been shown that most women with idiopathic hirsutism have abnormally high androgen metabolism in peripheral tissues (Such as Skin), making this largely a disorder of the peripheral compartment. Under these circumstances, normally circulating androgens like testosterone, are converted more efficiently to more potent androgens, like dihydrotestosterone. Dihydrotestosterone is the active intracellular androgen in the skin and is required for the expression of androgen effects. Thus, a high level of 5α-reductase in the skin, which converts testosterone to dihydrotestosterone, explains most of the abnormality in this type of hirsutism (idiopathic type). At present, we still use the term

"idiopathic" hirsutism to refer to those patients who have hirsutism with no changes in menstrual function. Circulating androgen levels are either normal or only minimally elevated, and the diagnosis of polycystic ovary syndrome and congenital adrenal hyperplasia have been excluded ***(Lobo, 1987).***

(2) Menstrual Disturbance:

The commonest presenting feature of PCOS patients is menstrual disturbances. Amenorrhea is an obvious indication of ovulatory failure, except in rare cases of uterine causes such as Asherman's syndrome. Oligomenorrheic cycles may sometimes be ovulatory, but the chance of conception is reduced and treatment is necessary. Women with normal menstrual cycles must be always tested for possible luteal deficiency ***(Goldzieher, 1981).***

Menstruation associated with anovulatory cycles may be at first heavy and painful and this dysfunctional bleeding may require treatment ***(Yen, 1991)***. Erratic and heavy periods are explained on the basis of the prolonged, unopposed estrogen stimulation on the endometrium which may occur in anovulatory cycles and it is common for women with PCOS to have an enlarged uterus with thickened endometrium which can be seen on ultrasound scanning of the pelvis ***(Frank et al., 1985)***.

Dysfunctional uterine bleeding in women with PCOS are particularly prevalent in women who are obese. There are at least two important factors which contribute to this phenomenon. Firstly, obese women produce more estrogen by extraglandular conversion of androgen

than do non-obese subjects. Obese women therefore have a greater excess of circulating estrone over estradiol concentrations than do lean women with PCOS. There is positive correlation of estrone/estradiol ratio with body mass index. Secondly, concentrations of SHBG are much lower in obese than lean women with PCOS with high significant negative correlation of SHBG with body mass index. This low concentrations of SHBG in obese patients with PCOS may be a result of hyper insulinmia which is associated with obese patients which has a direct inhibitory action on the liver. This leads to an increase in free fraction of estradiol in obese compared with lean women with PCOS. Dysfunctional uterine bleeding in obese women with PCOS) will often improve following weight loss ***(Kiddy et al, 1992)*** have shown that weight reduction improves menstrual pattern and in the women presenting with anovulatory infertility, may restore ovulation and fertility, and even if it fails to promote the return to cyclical ovarian activity, it may improve the response to therapy.

The increased bio-availability of estrogen may be the important etiological factor in the development of endometrial carcinoma. This illustrates the link between dysfunctional uterine bleeding and endometrial hyperplasia and then endometrial carcinoma **(*Lavecchia et al., 1982)***.

(3) Infertility:

A common symptom of polycystic ovaries is often infertility due to chronic oligo-ovulation or anovulation.

The restoration of ovulatory function assumes paramount importance. In this connection many treatment schedules have been proposed and implemented in an effort to circumvent the intrinsic block to ovulation and thus restore fertility ***(Donesky and Adashi, 1995).***

Infertility in polycystic ovary syndrome is usually primary, due to failure of ovulation, manifesting itself as irregular periods or amenorrhea, occasionally, the cycles may be ovulatory but associated with luteal phase insufficiency ***(Baird et al., 19S1)***.

It also seems possible mat there may be a further factor which reduce the chance of normal fertility in women with PCOS because there is a disparity between the rates of ..ovulation and pregnancy following induction of ovulation in PCOS ***(Frank et al., 1985)***.

It has been postulated that the raised follicular phase secretion of LH may cause premature resumption of meiosis in the oocyte, by antagonizing the action of the oocyte maturation inhibitor (OMI), the factor responsible for holding the oocyte in the diplotene stage of first meiotic division until just for ovulation **(*Jacobs, 1987)***.

Alternatively an endometrial defect may lead to suboptimal implantation. This is supported by the observation that women with PCOS have altered synthesis of endometrial prostaglandins which are important in normal implantation ***(Bonney et at., 1992)***.

(4) Obesity:

Obesity was originally thought to be one of the cardinal features of the clinical syndrome and crucial to the pathogenesis of the condition, but

is now recognized that many patients with PCOS have a normal body habitus ***(Goldzieher and Dizerga, 1985).***

Obesity was defined as body - mass index (BMI) > 25 Kg/m^2 where body-mass index was calculated as weight/height ^{2}(kg/m) ***(Eden et al., 1989).***

Obesity is known to depress sex hormone binding globulin level ***(Plymate et al., 1981)***, increasing the proportion of testosterone available; for peripheral conversion to estradiol. In addition, there is evidence to suggest that a disproportionately high body fat content cause a rise in extra-ovarian aromatase activity ***(Edman and MacDonald, 1988),*** thus increasing the role of conversion of androgen to estrogen. It is also well established that the obese develop hyperinsulinemia as a consequence of their body size.

There are low types of obesity: Gynecoid obesity or (Lower body obesity) and android or (central body obesity). If waist-to hip ratio greater than 0.85 indicates android fat distribution and if less than 0.75 means gynecoid fat distribution so, waist measurement is the smallest circumference between the rib cage and the iliac crests and the hip measurement is the largest circumference between the waist and thighs ***(Haffner et al.,1986).***

Rzbuffe-Service et al., (1989), found that android obesity in obese women with PCOS quite different from that for obese perimenopausal controls without PCOS which is of gynecoid type. Furthermore, they noted that obese and non obese women with PCOS had an identical pattern of distribution of fat.

Central body obesity (android) is the result of fat deposition in abdominal wall and visceral mesenteric locations. This fat distribution is associated with hyperinsulinemia, impaired glucose tolerance, diabetes mellitus, and an increase in androgen production rate resulting in decreased levels of sex hormone binding globulin and increased levels of free Testosterone and estradiol ***(Kirschner et al., 1990).***

Android obesity is associated with cardiovascular risk factors, including hypertension and unfavorable cholesterol-lipoprotein profiles. The adverse impact of excess weight in adolescents can be explained by the fact that deposition of fat in adolescence is largely central in location. Weight loss in women with lower body obesity is mainly cosmotic, where as loss of central body weight is more important for general health in that an improvement in cardiovascular risk is associated with loss of centeral body fat ***(Must et al., 1992)***.

** There are at least three possible mechanisms for a link between android obesity and hyper insulinemia **(*Speroff et al., 1994b).***

1. Android obesity is more active metabolically, resulting in higher free fatty acid concentration. Increasing free fatty acids lead to hyperglycemia.
2. Androgens may directly inhibit hepatic and peripheral insulin . action.
3. Androgens plus increased Free Fatty acids inhibit hepatic insulin extraction ***(Speroff et al., 1994b).***.

Differential Diagnosis Of PCOS

The diagnosis of PCOS may prove difficult in a few cases, and referral to a medical or reproductive endocrinologist may be valuable. Most gynaecologists have experience of using clomiphene citrate, but referral to an infertility expert is best when gonadotrophins are needed. Most patients with PCOS can be diagnosed and managed in general practice.

(I)Criteria for polycystic ovary syndrome and related disorders,

Criteria of the US National Institutes of Health

**** Polycystic ovary syndrome**

- Presence of menstrual abnormalities and anovulation
- Presence of clinical and/or biochemical hyperandrogenaemia
- Absence of hyperprolactinaemia or thyroid disease
- Absence of late-onset congenital adrenal hyperplasia
- Absence of Cushing's syndrome

**** Polycystic ovaries:**

- Presence of polycystic ovaries on ultrasound examination
- Absence of menstrual or cosmetic symptoms
- Absence of biochemical hyperandrogenaemia

**** Idiopathic hirsutism**

- Presence of excess hair growth

- Absence of biochemical hyperandrogenaemia

****Proposed criteria (European Society of Human Reproduction and Embryology and American Society for Reproductive Medicine)* As concluded at a **ESHRE/ASRM**-sponsored symposium on PCOS; 1 May 2003; Rotterdam, The Netherlands.

Polycystic ovary syndrome is diagnosed if there are any two of the following:

- ❖ Presence of polycystic ovaries on ultrasound examination
- ❖ Clinical or biochemical hyperandrogenism
- ❖ Menstrual dysfunction with anovulation

(II) Polycystic ovaries

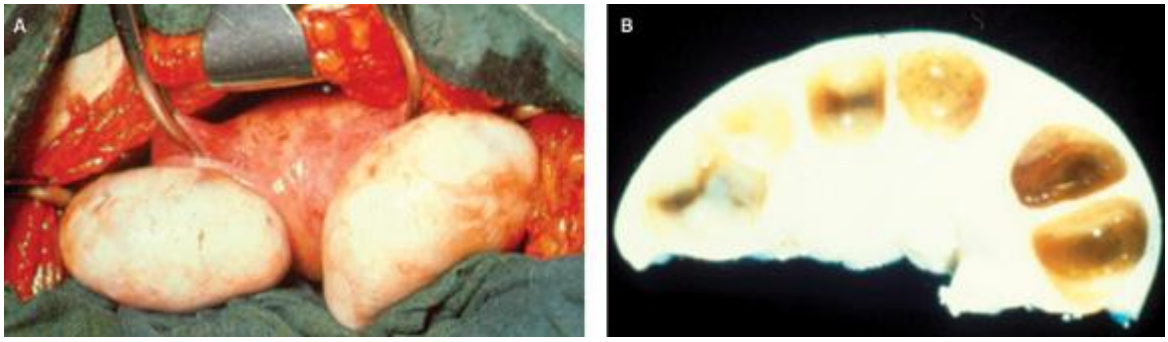
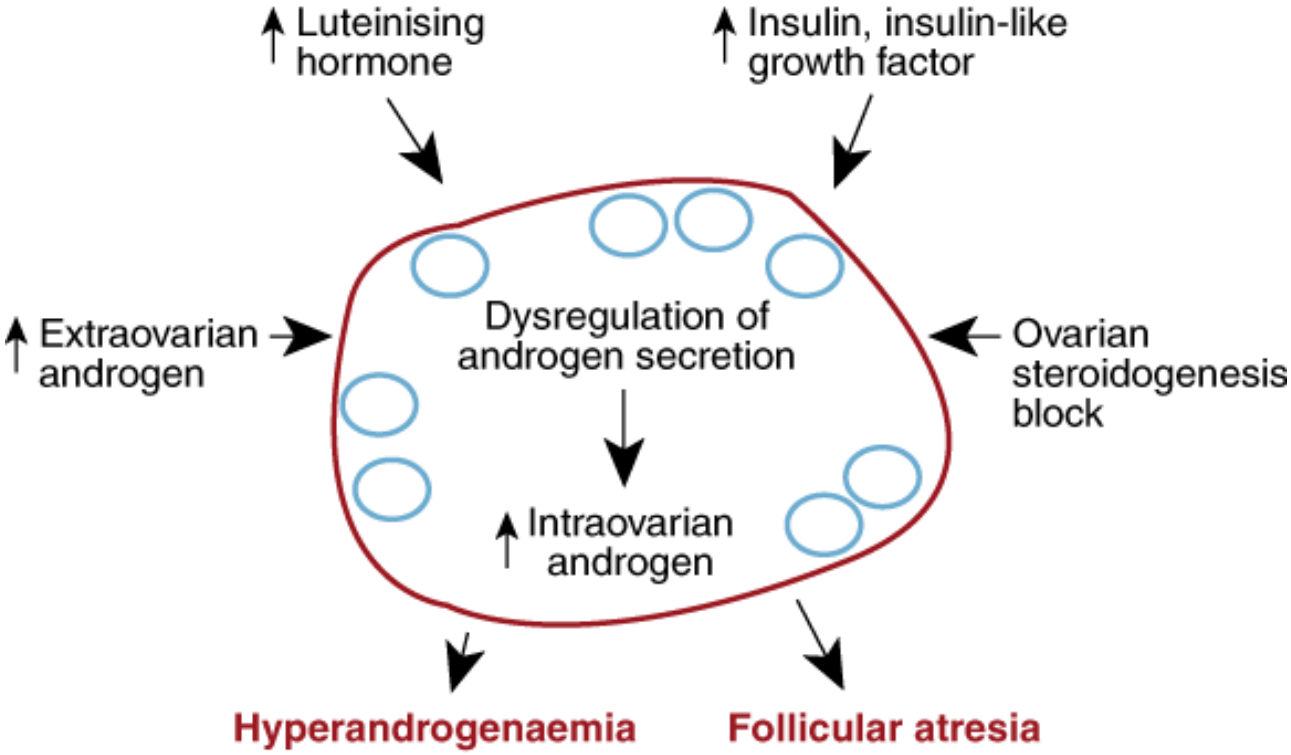


Figure "7"A: Polycystic ovaries, showing increased size and a smooth white surface reflecting thickening of the capsule. B: Section through polycystic ovary, showing multiple cysts with diameter < 10 mm arranged around the periphery of the ovary. The stroma is increased, and the ovary enlarged.

(III) Ovarian defect in polycystic ovary syndrome



Figur "8"

- The cardinal feature is functional ovarian hyperandrogenism.

V) Central obesity in PCOS

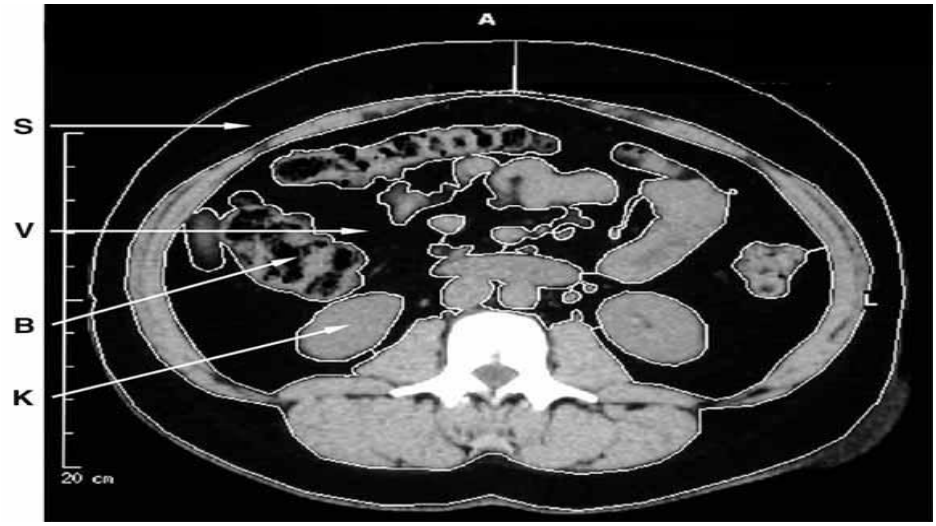


Figure "9 " **Computed tomography of the abdomen in polycystic ovary syndrome, showing subcutaneous (S) and visceral (V) fat, surrounding bowel (B) and kidneys (K).**

(IV) Manifestations of PCOS at different ages

Table "2"

In Utero	Peripuberty	Adolescence and adulthood	Ageing
Small baby syndrome: ➢ Intrauterine growth retardation	**Exaggerated adrenarche:** ➢ Increased levels of: # Adrenal androgen. # Insulin. ➢ Functional ovarian hyperandrogenism	**Polycystic ovary syndrome:** ➢ Anovulation. ➢ Hyperandrogenism. ➢ Polycystic ovaries. ➢ Obesity (50%).	**Metabolic Syndrome:** ➢ Diabetes. ➢ Hypertension. ➢ Dyslipidemia. ➢ Increased plasminogen activiator inhibitor-1.
Leads to V»» Long term health effects.	**Leads to »»** Precocious puerty	**Leads to »»** Reproductive disorders.	**Leads to »»** Metabolic effects.

(VI) Skin manifestations of polycystic ovary syndrome

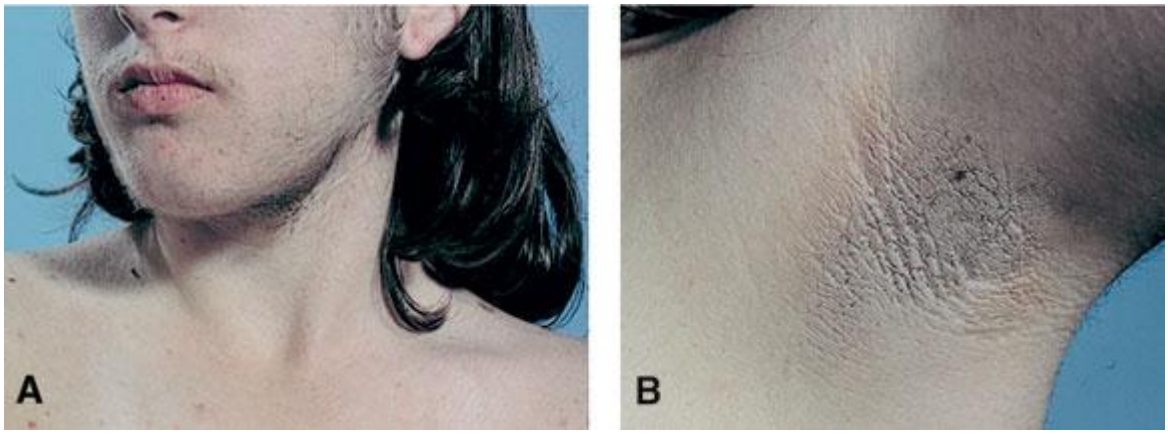


Figure "10 " Young woman with PCOS showing facial hirsutism (A) and axillary acanthosis nigricans (B). The latter is associated with severe insulin resistance and hyperinsulinaemia and is an occasional finding in PCOS (photographs courtesy Dr John Casey, St Vincent's Clinic, Sydney,

As noted previously, the diagnosis of PCOS is based on hyperandrogenism or chronic anovulation in the absence of specific pituitary and/or adrenal disease. The differential diagnoses of PCOS are listed in along with the tests needed to adequately assess for these possibilities. As is apparent, these disorders may cause some, but not all, features of PCOS. For instance, pregnancy, hypothyroidism, and hyperprolactinemia may all cause secondary amenorrhea but do not cause hirsutism; however, they need to be ruled-out ***(Azziz et al; 1994).***.

A careful history and physical examination, looking for other signs of those disorders that may not be a part of PCOS, must be performed. Symptoms of cold intolerance, dry skin, and increased fatigue (among others) may signify hypothyroidism, as would the presence of a goiter. Galactorrhea may or may not be present in women with hyperprolactinemia. Signs of virilization signify more significantly elevated androgen levels than those seen in PCOS , and may indicate an ovarian or adrenal tumor. Patients with Cushing's syndrome may be more apt to have hypertension, purple abdominal striae, prominent dorsal cervical fat pads, and a rounded, plethoric face, ***(Azziz et al; 1994).***

Late-onset congenital adrenal hyperplasia, even though relatively rare, deserves mention as it can mimic PCOS in all regards clinically. Congenital adrenal hyperplasia is due to one of a variety of enzymatic defects in adrenal steroido-genesis (which leads to increased levels of precursor hormones that have androgenic properties). The classic forms of these disorders involve complete enzymatic defects and present in newborn girls as ambiguous genitalia. More recently partial enzymatic defects in these same pathways have been shown to not present until

menarche and then with irregular menses and hirsutism mimicking PCOS. Measurement of the hormone preceding the enzymatic block is used to definitively diagnose these disorders. The most common form of late-onset congenital adrenal hyperplasia is due to 21-hydroxylase deficiency and, as such, is often the only type tested for in the differential diagnosis of PCOS. The interested reader is referred to the review by Azziz and colleagues for a more complete discussion of these disorders ***(Azziz et al; 1994).***

Laboratory Diagnosis of PCOS

Biochemical evaluations should look for supporting evidence of PCOS (hyperandrogenism and IR) and rule out the other disorders described above. All of the tests (with the exception of the 24-hour urine free cortisol) should be performed in every patient. It should be noted that direct testing for IR is fraught with difficulties and there are many methods in use, ***(Yokoyama et al; 2003).***

Only the simplest, fasting glucose-to-insulin ratio is mentioned for simplicity. It should be noted that the use of the fasting glucose-to-insulin ratio to measure IR has been studied primarily in obese and lean euglycemic, non-Hispanic white adult women and in obese and lean euglycemic, Hispanic adolescents ***(Silfen et al;' 2001).***

It is likely not a valid marker in patients with impaired fasting glucose or impaired glucose tolerance, and assessing for IR in patients who are not euglycemic is likely a moot point. Furthermore, none of the tests for IR are extremely sensitive or specific, and the argument can be made that none are needed. On the contrary, assessment of fasting lipids and glucose may be enough. Lastly, a 2-hour oral glucose tolerance test

may be a better predictor of IR than fasting glucose, and it is extremely useful in categorizing patients' risk of type 2 diabetes mellitus, which may affect therapeutic decisions , ***(Carnevale et al; 2003).***

** HORMONAL PROFILE

1 . Testosterone

- - A total testosterone is likely to be more reliable than a free testosterone given the difficulties seen with many of the assays used for the latter, ***(Rosner et al; 2001).***
- - Testosterone values may be normal in PCOS.
- - Oral contraceptives will lower total testosterone, and interpretation in this setting is difficult (3 months off oral contraceptives is best to get a "true" testosterone value).

- - Most testosterone values in PCOS will be ≤150 ng/dL (≤5.2 nmol/L).
- - Testosterone values of ≥200 ng/dL (≥6.9 nmol/L) warrant consideration of an ovarian or adrenal tumor, ***(Derksen et al; 1994).***

2 . Dehydroepiandrosterone-sulfate (DHEA-S)

- - DHEA-S values may be normal or slightly elevated in PCOS.
- - DHEA-S values ≥800 µg/dL (21.7 µmol/L) warrant consideration of an adrenal tumor ***(Derksen et al; 1994).***

3 . Prolactin- Mild hyperprolactinemia has been reported in 5% to 30% of patients with PCOS ***(Franks 1989).***

Prolactin is generally only 50% above the upper limit of normal.[21] Furthermore, hyperprolactinemia is most often transient, with perhaps only 3% to 7% of hyperprolactinemic PCOS patients having persistently elevated prolactin levels, ***(Bracero et al; 2001).***

- Thus, it is now felt that PCOS and hyperprolactinemia are independent disorders. If normalization on re-sampling does not occur, then an assessment for other causes should be undertaken (including pituitary magnetic resonance imaging).
- - Patients with prolactinomas may have polycystic ovaries on ultrasound ***(Franks 1995).***

4 . 17-hydroxyprogesterone

- - A morning, fasting, unstimulated level of <200 ng/dL (<6 nmol/L) in the follicular phase reliably excludes late-onset 21-hydroxylase deficiency.
- - Further evaluation of levels ≥200 ng/dL involves adrenocorticotropic hormone (ACTH)-stimulation with an intravenous 250 µg dose and a 30 minute value (stimulated values ≥ 1,000 ng/dL (≥30 nmol/L) confirm the diagnosis***) (Azziz et al; 1994).***
- - Oral contraceptives and glucocorticoids can affect values.

5 . 24-hour urine free cortisol

- - Mild elevations can be seen in PCOS with values >2 times the upper limit of normal more consistent with Cushing's syndrome.
- - For mild elevations a dexamethasone-suppression, corticotropin-releasing hormone stimulation test is needed to distinguish mild

Cushing's syndrome from pseudo-Cushing's, ***(Yonovski et al; 1998).***

- - Interpretation of serum (but not urine) cortisol levels in patients on oral contraceptives is problematic as cortisol-binding globulin may be increased falsely elevating the values (it is especially important that oral contraceptives be discontinued before dynamic testing is performed) ***(Yonovski et al; 1998).***

6 . Luteinizing hormone/follicle stimulating hormone (LS/FSH) ratio

- - A ratio ≥2.0 is suggestive of PCOS but is not highly sensitive or specific.
- - Gonadotropin levels are affected by oral contraceptives ***(Yonovski et al; 1998).***

**** A list of other laboratory tests that may help to identify patients with PCOS is provided in Table " 3 " :**

TABLE "3 "
Laboratory Investigation of PCOS

Test	*Normal value*	*Purpose*
b-hCG	< 5 mIU per mL (< 5 IU per L)	Exclude pregnancy
TSH	0.5 to 4.5 µU per mL (0.5 to 4.5 mU per L)	Exclude thyroid dysfunction
Prolactin	< 20 ng per mL (< 20 µg per	Exclude

	L)	hyperprolactinemia
Testosterone (total)	< 20 ng per dL (< 0.7 nmol per L)	Exclude androgen-secreting neoplasm
Testosterone (free)	20 to 30 years--0.06 to 2.57 pg per mL (0.20 to 8.90 pmol per L) 40 to 59 years--0.4 to 2.03 pg per mL (1.40 to 7.00 pmol per L)	Establish diagnosis or monitor therapy
DHEAS	600 to 3,400 ng per mL (1.6 to 9.2 µmol per L)	Exclude androgen-secreting neoplasm
Androstenedione	0.4 to 2.7 ng per mL (1.4 to 9.4 nmol per L)	Establish diagnosis
17a-hydroxyprogesterone	Follicular phase < 2 µg per L (6.1 nmol per L)	Exclude NCAH
Fasting insulin	< 20 µU per mL (< 144 pmol per L)	Exclude hyperinsulinemia
Fasting glucose	65 to 119 mg per dL (3.6 to 6.6 mmol per L)	Exclude type 2 diabetes or glucose intolerance
Fasting glucose: insulin ratio	>= 4.5	Exclude insulin resistance
Cholesterol (total)	150 to 200 mg per dL (1.5 to 2 g per L)	Monitor lifestyle changes
HDL cholesterol	35 to 85 mg per dL (0.9 to 2.2 mmol per L)	Monitor lifestyle changes

LDL cholesterol	80 to 130 mg per dL (2.1 to 3.4 mmol per L)	Monitor lifestyle changes
Pelvic ultrasonography		Monitor lifestyle changes
Endometrial biopsy	Negative for hyperplasia/malignancy	Exclude malignancy or hyperplasia

NOTE: *Diagnosis of PCOS established by exclusion of other causes of oligomenorrhea or hyperandrogenism. Other tests may be of benefit in monitoring therapy.*

OS = polycystic ovary syndrome; b-hCG = beta subunit human chorionic gonadotropin; TSH = thyroid-stimulating hormone; DHEAS = dehydroepiandrosterone sulfate; NCAH = nonclassic adrenal hyperplasia; HDL = high-density lipoprotein; LDL = low-density lipoprotein.>

Imaging Diagnosis Of PCOS

Pelvic Ultrasonography

Pelvic ultrasonography may be very helpful in the evaluation as well, but polycystic ovaries are not specific for PCOS with over 20% of "normal" women having this finding, ***(polson et al; 1988).***

The number of follicles and ovary volume are both important in the ultrasound evaluation. The criteria for PCOS put forth by ***Adams et al (1985).*** are the most often cited: the presence of ≥10 cysts measuring 2–8 mm around a dense core of stroma or scattered within an increased amount of stroma**.**

A recent proposal to modify these criteria has been put forth by Jonard et al.: "increased ovarian area (>5.5cm^2) or volume (>11 mL) and/or presence of ≥12 follicles measuring 2 to 9 mm in diameter (mean of both ovaries)" ***(Jonard et al; 2003).***

These criteria had a specificity of 99% and a sensitivity of 75% for the diagnosis of PCOS ***(Jonard et al; 2003).***

The approach to laboratory and ultrasound evaluations in the diagnosis of PCOS varies widely without any consensus even among experts in the field. Indeed, the diagnosis of PCOS in Europe does not require any hormonal testing, with great importance placed on the finding of polycystic ovaries on ultrasound ***(Homburg et al; 2002).***

This is in stark contrast to the National Institute of Health conference in 1990 which did not include ultrasound evidence of polycystic ovaries in the diagnostic criteria. What is needed is a simple consensus that is easy to implement for the clinician trying to diagnose this highly prevalent disorder with important health consequences ***(Dunaif A 2001).***

Perhaps this 'clinical' consensus should be different than that used in the research setting. An extremely practical proposal has recently been put forth for the diagnosis of PCOS by Homburg ***(Homburg et al; 2002).***

In this proposal any one of the four classic symptoms of PCOS (menstrual disturbance, hirsutism, acne or anovulatory infertility) should lead to an ultrasound evaluation of the ovaries. If polycystic ovaries are found, the diagnosis is confirmed. If the ovarian morphology is normal, then biochemical testing is undertaken. If any one or more of the following are noted, the diagnosis is confirmed: elevated LH, fasting

glucose/insulin <4.5, and/or elevated testosterone or free androgen index (in the absence of late-onset congenital adrenal hyperplasia). The argument could be made, however, that the exclusion of the other conditions listed in table 3♠ should be a part of such guidelines. That said, proposals such as the one put forward by Homburg are the first steps toward a much needed, simple, and unified set of diagnostic guidelines for the clinician.

Introduction

The metabolic syndrome (MBS) is a disorder which is composed of the clustering of several metabolic abnormalities including glucose abnormalities, dyslipidemia, obesity and hypertension, ***(Alberti et al 1998).***

This syndrome was first proposed by Reaven, (Reaven G 1988), and several studies have been reported in several names, the syndrome X, the insulin resistance syndrome, and the dysmetabolic syndrome, for instance, ***(Alberti et al 1998 , Groop et al 2001).***

The pathophysiology of MBS is IR, ***(Reaven et al 2001)***. Normally, IR state results in compensatory hyperinsulinemia. Both IR and hyperinsulinemia have effects on the several aspects of metabolism. It is well-recognized that IR is a cause of type 2 DM and glucose intolerance, ***(Lillioia et al 1993),*** and dyslipidemia which comprises of high triglyceride and low high density lipoprotein-cholesterol (HDL-C) levels, ***(Third report of the NCEP on detection , evaluation, & treatment of high cholesterol 2001 , World Health Organization 2004).***

More recently, there have been reports that insulin has inducing pressure effects including increased sympathetic activity, renal sodium retention, and smooth muscle cell proliferation, ***(Saward et al 1996).***

Also, IR may impair the endothelial cell production of nitric oxide (N0), a substance that can stimulate some factors to cause vasodilatation, ***(Yki-Jaryinen 2003).***

It can be seen that IR and its secondary metabolic abnormalities are the risk factors of cardiovascular disease (CVD). There have been reports that insulin excess is associated with CVD in non-diabetic individuals, (***UWaifo et al 2003)***, and increases cardiovascular risk in patients with type 2 DM, (***Fontbonne et al 1991).***

Certainly, it is well-recognized that type 2 DM is the most important risk factor for CVD, ***(Haffner et al 2003).***

Interestingly, impaired glucose metabolism (IGT) is reported as a risk factor for CVD***,(Haffner et al 2003).*** In addition, obesity, hypertension, and dyslipidemia, the components of MS are also the risk factors for CVD, ***(Austin et al 2000, Sowers 2003).***

PCOS is the most common form of anovulatory infertility. Its association with menstrual disturbance and altered hormonal parameters leads many affected women of reproductive age to attend a gynaecology or infertility clinic, ***(Talbott et al; 1995)***.

The aetiology of the condition is unknown, but recent evidence suggests that the principal underlying disorder is one of insulin resistance, with the resultant hyperinsulinaemia stimulating excess ovarian androgen production. Associated with the prevalent insulin resistance, these women exhibit a characteristic dyslipidaemia and a predisposition to non-insulin dependent diabetes and cardiovascular disease in later life. Thus, polycystic ovary syndrome seems to have many of the hallmarks of the metabolic syndrome ***(Talbott et al; 1995)***.

In 2001, the Adult Treatment Panel III (ATP III), of the National Cholesterol Education Program proposed criteria for diagnosing what

they designated the metabolic syndrome , ***(National Cholesterol Education Program NCEP 2002).*** Since the original report by Ford et al. ***(Ford vet al; 2002)*** in 2002 describing the prevalence of the metabolic syndrome in the United States, multiple papers have been published addressing the same issue. As an example of this phenomenon, I cite 14 articles, that represent a small sample of those published on this topic in 2004; they were based primarily on retrospective analyses of population-based studies, conducted in several countries, with experimental data gathered for a variety of different reasons, in groups differing in terms of age, sex, and ethnicity. Although this burst of creative activity has led to an enormous amount of published data, it is not clear that it has led to the delivery of any new information of significant utility to the practicing clinician. In fact, as will be discussed subsequently, if taken at face value, there is a real possibility that use of the ATP III criteria could do more harm than good. At the least, it might be useful to take a somewhat skeptical look at the clinical implications of implementing the diagnostic criteria proposed by the ATP III, ***(Cheng T 2004, Weiss et al 2004, Kinder et al 2004)***.

Defintion Of Metabolic Syndrome

The establishment of criteria for diagnosing what the ATP III report termed the metabolic syndrome represented an effort to acknowledge the importance of resistance to insulin action, and its consequences, as increasing the risk of cardiovascular disease (CVD) ***(National Cholesterol Education Program NCEP 2002).***

The ATP III recognized the importance as CVD risk factors of what they called a "constellation of lipid and non-lipid risk factors of

metabolic origin," designated this cluster as the metabolic syndrome, and stated that "this syndrome is closely related to insulin resistance." Table 4✦ lists the five criteria selected by the ATP to identify individuals with the metabolic syndrome [abdominal obesity, impaired fasting glucose, high triglyceride (TG) and low HDL-cholesterol (HDL-C) concentrations, and increased blood pressure], and reflects their view that insulin resistance is at the root of the problem. The primary goals of the ATP III in establishing criteria for making the diagnosis of the metabolic syndrome to identify individuals at increased CVD risk and to use this information to initiate lifestyle changes to decrease this risk ***(National Cholesterol Education Program NCEP 2002).***

Table "4": ATP III criteria for diagnosing the metabolic syndrome.

- Fasting blood glucose higher than 110 mg/dL
- Fasting triglyceride greater than 150 mg/dL
- Fasting HDL (good cholesterol) lower than 50 mg/dL
- Blood pressure greater than 130 over 80
- Waist circumference greater 35 inches (apple shape)

(National Cholesterol Education Program NCEP 2002).

The individual criteria listed in Table 4✦ appear to have been selected because they tend to cluster together as well as to occur more commonly in insulin-resistant individuals ***(Reaven et al; 2003).***

In addition, they all have been associated with increased CVD risk ***(Kannel et al; 1996, Gaziano et al; 1997).***

However, before focusing on the individual components that make up the diagnostic criteria for the metabolic syndrome, some general comments about the deliberations that led to their creation are worthy of note. Perhaps the most crucial issue is that the diagnostic criteria for the metabolic syndrome did not result from a prospective study and do not represent the outcome of an evidence-based process, but are a reflection of the best estimates of a panel of "experts". Furthermore, not only are the cut points for the five chosen criteria arbitrary, there is no reason to believe that the individual elements of the metabolic syndrome are equally reflective of either the presumed basic defect or the risk of CVD. Indeed, it is not clear what led to the decision to select five criteria (why not four or six?), nor why satisfying any three of five arbitrary criteria has more clinical utility than any two others. In light of the above considerations, there is ample reason to question the clinical utility of making a positive (or negative) diagnosis of the metabolic syndrome ***(Kannel et al; 1996, Gaziano et al; 1997).***

Furthermore, before critically examining the criteria proposed for making the diagnosis of the metabolic syndrome, it is essential to emphasize that the report of the ATP III focused entirely on the role of insulin resistance as increasing risk of CVD. It is now clear, however, that a variety of abnormalities and clinical syndromes are more likely to occur in insulin-resistant individuals. Specifically, in addition to CVD, insulin-resistant individuals are at increased risk to develop type 2 diabetes, essential hypertension, nonalcoholic liver disease, polycystic ovary syndrome, certain forms of cancer, and sleep apnea. ***(Reaven et al; 2004, Kim et al 2004).***

TABLE "5" DEFINITION OF METABOLIC SYNDROME		
NCEP	***WHO***	***MODIFIED WHO***
Any three of the following criteria: * **Fasting Blood Glucose** ≥ 110mg / dl * **Hypertension:** ≥ 130 mmhg Systolic Blood Pressure, or ≥ 85 mmhg Diastolic Blood Pressure. * **Obesity:** Waist circumference > 40 inches for males and 35 inches for female. * **Elevated triglycerides**: ≥ 150 mg l dl. * **Low HDL:** < 40 mg l dl in males and 50 mg l dl in females.	**Insulin resistance** (under hyperinsulinemia , eugenic condition). **Plus two of the following criteria:** **Hypertension:** ≥ 160/90 mmhg Or controlled with drug treatment. **Obesity:** BMI ≥ 30 kg/m2 or Waist to Hip ratio > 0.9 for males, and > 0.85 for females. **Elevated triglycerides:** ≥ 150 mg l dl. Low HDL: < 35 mg l dl in males and 40 mg l dl in females. **Microalbiminuria:** > 20 µg / min or albumin-to-creatinine ratio ≥ 20 mglg.	**Hyperinsulinemia:** Upper quartile of population or Fasting Plasma Glucose ≥ 110 mg l dl. **Plus two of the following criteria:** **Hypertension:** ≥ 140/90 mmhg Or controlled with drug treatment. **Obesity:** BMI ≥ 30 kg/m2 or Waist to Hip ratio > 0.9 for males, and > 0.85 for females. **Dislipidemia** with either or both Elevated triglycerides: ≥ 150 mg l dl. **Low HDL:** < 35 mg l dl in males and 40 mg l dl in females.
Modified as described in the Kuopio study.		

A major advantage of the NCEP definition is its ease of application. For instance, while neither sensitive nor specific as an indicator of insulin resistance, fasting glucose testing identifies further developed abnormalities of glucose regulation and can readily be performed in clinical practice and large clinical trials. For the WHO definition, measurement of insulin resistance requires a cumbersome clamp study, which has confounded its use. Thus, major epidemiological

studies such as the European Group for the Study of Insulin Resistance and the Botnia study in Finland and Sweden used widely applicable surrogate markers of insulin resistance, such as fasting glucose and insulin levels ***(Balkau et al 1999),*** or glucose tolerance tests, ***(Isomao et al 2001).***

Additionally, newer data have allowed subtle refinements in cut-off criteria based on outcomes research. Just as the blood glucose level used to define diabetes was lowered in 1997 based on outcomes ,***(Expert committee on the diagnosis and classification of DM 1997).***

Definitions of hypertension in the metabolic syndrome have recently been lowered, ***(Chobanian et al 2003).***

Finally, waist circumference has replaced BMI as a marker of obesity because of its better correlation with intra-abdominal visceral adipose tissue and worsened cardiovascular outcomes, ***(Pouliot et al 1994).***

Using data from the Kuopio Finnish cohort, the NCEP ATP-III and the WHO modified definitions of the metabolic syndrome were both validated in a large epidemiological study that found up to four times higher coronary heart disease (CHD) mortality in patients with the metabolic syndrome, ***(Lakka et al 2002).***

The stated purposes of the NCEP ATP-III guidelines were to maintain the original ATP-I and -II goal of primary prevention of CHD in people with high LDL cholesterol with the new focus on people with multiple risk factors, such as those with the metabolic syndrome, (***Executive summary of the third report of NCEP 2001).*** Women with PCOS are such a group.

Prevalance Of Metabolic Syndrome

Using the WHO definition and data from the national health and nutrition examination survey III (NHANES III) and the NCEP ATP III criteria, the age adjusted prevalence of the MBS in the USA is currently estimated at 24% and increases to 44% in adults who are over 60 years ***(NCEP 2001, Ford et al; 2002).***

The prevalence of two or more MBS components is 43.9%, showing that a large group is at risk for its development. Based on the data from the 2000 US census, an estimated 47 million US residents have the MBS ***(Ford et al; 2002).***

There is a 3.2 relative risk of acute coronary events in subjects with characteristics of the MBS (body mass index $\geqslant$25.0 kg/m^2 and waist to hip ratio $\geqslant$0.91) ***(Lakka et al; 2002).***

In the women's angiographic vitamin and oestrogen trial the prevalence of the MBS was 60% and clinical cardiovascular events were significantly more frequent compared with those without MBS ***(Hsia et al; 2003).***

However, going throughout the studies recently published the prevalence of the MBS varies from 7% to 84% ***(Balkau et al; 2002 , Isomaa et al; 2001).***

The criteria involved in the MBS, especially type 2 diabetes mellitus, as well as other parameters such as age, sex, study's populations, and ethnic differences may explain these differences. For example, the prevalence of the MBS among American adults seems to be the highest in

Mexican American women (33%) and the lowest in white American women (21%) ***(Meigs et al; 2003).***

The prevalence of coronary heart disease or cardiovascular disease also varies. These variations suggest that some people have a genetic predisposition that leaves them more susceptible to the development of the metabolic disturbances produced by the Western lifestyle. An example of this can be found in the Pima Indians. The group that moved to Arizona 700–1000 years ago and progressively adopted a Western diet, by the age of 35 developed obesity in >85% and diabetes in >50% in contrast with the group who still lives in Mexico and is characterised by a traditional lifestyle, where obesity and diabetes do not seem to be an important health problem ***(Ravussin et al; 1994).***

The MBS is a multifactorial complex trait that is influenced by both environmental and genetic factors. Mutations and polymorphisms in the genes associated with insulin resistance, adipocyte abnormality, hypertension, lipid abnormalities may underlie the aetiological basis of the MBS. The diagnosis of the MBS seems to identify substantial additional cardiovascular risk above and beyond the individual risk factors. Therefore, the clinical diagnosis of the MBS may be a valuable tool for identification of the elusive high risk patients ***(Ravussin et al; 1994).***

Pathophysiology Of Metabolic Syndrome

Good evidence supports the hypothesis that decreased peripheral insulin sensitivity and consequent hyperinsulinaemia are pivotal in the pathogenesis of polycystic ovarian syndrome ***(Dunai et al 1997).***

Peripheral insulin resistance is most evident in overweight patients: obesity and polycystic ovarian syndrome each seem to have a separate and synergistic relation with insulin resistance ***(Dunai 1997).***

The exact mechanism(s) for insulin resistance is uncertain, but a post-receptor defect in adipose tissue has been identified ***(Dunaif 1997).***

Despite insulin resistance in adipose and skeletal muscle, the ovary remains relatively sensitive to insulin, and both insulin and insulin-like growth factor 1 have stimulatory effects on thecal androgen production ***(Bergh et al; 1993).***

In fact, some lean women with polycystic ovary syndrome, who may not have insulin resistance and therefore hyperinsulinaemia, may show enhanced ovarian sensitivity to insulin. The relative excess of insulin or enhanced ovarian sensitivity to insulin, in combination with an elevated luteinising hormone concentration, brings about thecal hyperplasia, increased androgen secretion, arrest of follicular development, and therefore anovulation along with menstrual disturbance ***(Bergh et al; 1993).***

Insulin also acts on the liver to inhibit the production of sex hormone binding globulin and insulin-like growth factor 1 binding protein. A reduction in sex hormone binding globulin leads to an increase in the biologically available free testosterone. Thus, insulin resistance not only increases secretion of ovarian androgens but also promotes an increase in the proportion of free (active) hormone. Similarly, inhibition of production of insulin-like growth factor 1 binding protein results in an increased concentration of circulating free insulin-like growth factor 1, further enhancing ovarian androgen production ***(Cataldo et al; 1997).***

Current consensus suggests that the ovary is the principal site of excess androgen production, but some women with polycystic ovary syndrome may have an adrenal contribution to the increased androgen production. The mechanisms for this remain obscure and are almost certainly multifactorial, ***(Gonzalez et al; 1997).***

*****The conference on the definition of the metabolic syndrome identified 3 potential etiologic categories:***

(1) Obesity and disorders of adipose tissue.

(2) Insulin sensetivity.

(3) A constellation of independent factors (eg, molecules of hepatic, vascular, and immunologic origin). that mediate specific components of the syndrome ***(Grundy et al; 2004).***

Both genetic and acquired causes were determined to play a role in each ***(Grundy et al; 2004).***

Obesity and disorders of adipose tissue: In clinical and epidemiological studies, obesity is strongly associated with all cardiovascular risk factors. Adipose tissue is recognized as a source of several molecules that are potentially pathogenic: excess nonesterified fatty acids, cytokines (tumor necrosis factor-α), resistin, adiponectin, leptin, and PAI-1. Visceral adipose tissue may be particularly active in producing several of these factors. However, the mechanisms underlying the association between abdominal obesity (particularly visceral obesity) and the metabolic syndrome are not fully understood and likely are complex. It has been assumed that obese adipose tissue releases an excess of fatty acids and cytokines that induce insulin resistance; however, there is growing

recognition that this concept, although undoubtedly containing truth, is an oversimplification of the interactions among obesity, body fat distribution, and cardiovascular risk factors, ***(Grundy et al; 2004).***

Insulin sensetivity The second pathogenic category, insulin resistance, is widely believed to be at the heart of the metabolic syndrome, even though there is as yet little clinical trial evidence that a reduction in insulin resistance will substantially improve any of the components of the metabolic syndrome other than glucose intolerance. Thus, the mechanistic link between insulin resistance and most of the components of the metabolic syndrome remains unclear. Although insulin resistance is strongly associated with atherogenic dyslipidemia and a proinflammatory state, it is less tightly associated with hypertension and the prothrombotic state. Finally, some data support the concept that insulin resistance or its associated hyperinsulinemia are independent risk factors for CVD, but this association has not yet been confirmed in controlled studies ***(Grundy et al; 2004).***

Much of the heterogeneity in the manifestation of the metabolic syndrome may therefore be due to the fact that many of the component factors are regulated independently of insulin resistance. Lipoprotein metabolism is regulated by genetic factors as well as by diet composition, and both can worsen atherogenic dyslipidemia. Blood pressure regulation is similarly complex and affected by dietary factors, physical activity, and renal/adrenal organ function. Only some persons with obesity and/or insulin resistance develop type 2 diabetes; for diabetes to appear, independent defects in beta-cell function must be present ***(Grundy et al; 2004).***

Other important modifiers also influence clinical expression of the metabolic syndrome. For example, physical inactivity promotes the development of obesity and modifies muscle insulin sensitivity. Aging is commonly accompanied by a loss of muscle mass and by an increase in body fat, particularly accumulation of fat in the abdomen; both changes can increase insulin resistance. Moreover, recent studies suggest that aging is accompanied by specific defects in fatty acid oxidation in muscle, also enhancing insulin resistance. Hyperandrogenemia has been associated with insulin resistance in women with polycystic ovary disease. Furthermore, mild hypercorticoidism has been implicated in development of abdominal obesity ***(Grundy et al; 2004).***

Dyslipidemia In Metabolic Syndrome

Dyslipidaemia, the hallmark of the MetS, is summarised as

(a) increased flux of free fatty acids.

(b) raised TG values.

(c) low high density lipoprotein (HDL) cholesterol values.

(d) increased small, dense low density lipoprotein (LDL) values.

(e) raised apolipoprotein (apo) B values***, (Ginsberg et al; 2000).***

Dyslipidaemia is widely established as an independent risk factor for cardiovascular disease, ***(Genest et al; 2000).***

Low HDL cholesterol and hypertriglyceridaemia have been found to be independently and significantly related to myocardial infarction/stroke in patients with MBS ***(Ninomiya et al; 2004).***

Additionally, a combination of high fasting glucose and low HDL cholesterol were shown to have primary predictive ability for coronary heart disease ***(Anderson et al; 2004).***

Moreover, in the study of Sacco and colleagues, the role of HDL cholesterol values, as an important modifiable stroke risk factor, was further supported ***(Sacco et al; 2001).***

The dyslipidaemia in MetS patients may be caused by a combination of overproduction of very low density lipoprotein (VLDL) apo B-100, decreased catabolism of apo B containing particles, and increased catabolism of HDL-apo A-I particles. These abnormalities may be the consequence of a global metabolic effect of insulin resistance. Although the underlying mechanisms for this pattern are not fully understood, a cascade of events has been proposed for the observed phenotype, which ties in with all of the abnormalities present in these disorders . ***(Sacco et al; 2001).***

Increased free fatty acids

The primary defect is probably focused in the inability to incorporate the free fatty acids to TGs by the adipose tissue (inadequate esterification) ***(Ginsberg et al; 2000).***

This results in reduced fatty acid trapping and consequent retention by the adipose tissue. The insulin resistance also causes reduced retention of free fatty acids by the adipocytes. Both these abnormalities lead to increased flux of free fatty acids back to the liver (fig 13). However, some studies have shown that hepatic fatty acid metabolism is required for the development of insulin resistance ***(Ginsberg et al; 2000).***

Adipose tissue, for a long time, was regarded as a comparatively passive side of energy storage (accumulated in the form of TGs). However, recent studies show that adipose tissue is an endocrine organ producing various proteins (adipocytokines) ***(Trayhurn et al; 2004).***

Adipocytokines include leptin, angiotensinogen, tumour necrosis factor α, interleukin 6, plasminogen activator-inhibitor 1, transforming growth factor ß, adipsin, adiponectin, resistin. These proteins are increased (with the exception of adiponectin, which decreases) in obesity and, at least under experimental settings, possibly can induce obesity related insulin resistance or diabetes ***(Beltowski et al; 2003, Haliuzik et al; 2004).***

Additionally, adipose tissue is a prominent source of cholesteryl ester transfer protein ***(Drayna et al; 1987).***

Cholesteryl ester transfer protein is an important determinant of lipoprotein composition because of its capacity to mediate the transfer of cholesteryl esters from cholesteryl ester rich lipoproteins to TG rich lipoproteins in exchange for TGs ***(Marlon et al; 1999).***

In obese subjects, cholesteryl ester transfer protein activity and mass are increased ***(Arai et al; 1994).***

Increased Triglycerides:

Increased flux of free fatty acids from the periphery to the liver in the insulin resistant state stimulates hepatic TG synthesis, which in turn promotes the assembly and secretion of TG containing VLDL ***(Gorter et al; 2004***), as well as the apo B production in the liver ***(Lewis et al; 1993).***

Under normolipidaemic conditions in humans, VLDL secretion is affected by TG and cholesterol availability and recent studies suggest an association between cholesterol synthesis and production of smaller VLDL particles ($VLDL_2$) ***(Princen et al; 2003).***

While insulin suppresses the formation of large VLDL particles, $VLDL_1$ does not have any impact on the production of the smaller $VLDL_2$ fraction ***(Malmstrom et al; 1997).***

When insulin resistance occurs, the high insulin values make the liver resistant to the inhibitory effects of insulin on VLDL secretion ***(Lewis et al; 1993).***

Visceral obesity and increased intra-abdominal fat have been shown to precede development of insulin resistance ***(Goldstein et al; 2003).***

Increasing insulin resistance is proposed to be the precursor for two events. Firstly, in the presence of insulin resistance, the visceral adipocyte is more sensitive to the metabolic effects of the lipolytic hormones glucocorticoids and catecholamines ***(McFarlane et al; 2001).***

This hormonal lipolytic activity produces an increased release of free fatty acids into the portal system, which serves as hepatic substrate to assemble TGs and TG rich VLDLs. Secondly, increasing insulin resistance leads to increased production of apo B, the major protein of LDL, and as a consequence to the increased synthesis and secretion of TG containing VLDL cholesterol particles ***(Kwiterovich et al; 2002).***

Experiments in cell cultures suggest that VLDL assembly is complex and entails a two step process ***(Malmstrom et al; 1997).***

Firstly, a small lipoprotein particle containing little TG is formed in the rough endoplasmic reticulum, and secondly, the bulk of the TG core is added to this at the junction of the rough and smooth endoplasmic reticulum. It is possible that the release of small VLDL follows the addition of a comparatively small quantity of TG (or of cholesteryl ester) to the nascent particle while large VLDL is formed by the addition of a substantial TG core in a second quantum step. In subjects with a low circulating concentration of TG, the liver has insufficient TG to assemble a $VLDL_2$ sized particle and intermediate density lipoprotein/LDL are secreted. The substantial decrease in clearance rates of both $VLDL_1$ and $VLDL_2$ appears as plasma TG rises leading to accumulation of large VLDL particles ***(Packard et al; 2003).***

This fall off of clearance rates is likely to reflect the rates of lipolysis and could be attributable to a change in lipoprotein lipase activity (decreased in insulin resistance state) and other factors such as the apoC-II content or the apoCII/CIII ratio (modulators of lipoprotein lipase activity) in VLDL ***(Ginsberg et al; 1986).***

However, studies in animals and humans are needed in which the impact of hepatic TG synthesis on VLDL TG production is carefully assessed. It is probable that the causes of raised TG values in the MBS are multifactorial and not simply a function of increased free fatty acid flux to the liver***(Ginsberg et al; 1986).***

Small dense LDL:

In the insulin resistant state, the LDL levels are usually within normal limits or only mildly raised; however the LDL particle is often of abnormal composition (small, dense LDL). The underlying abnormality

causing small dense LDL is hypertriglyceridaemia. It has been found that small dense LDL is not seen until plasma TG levels exceed 1.5 mmol/l ***(Packard et al; 2003).***

Under these conditions, large TG rich VLDL ($VLDL_1$) molecules accumulate. When VLDL is lipolysed by lipoprotein lipase, a population of LDL particles with changed apo B conformation is produced. These particles fail to bind efficiently to LDL receptors and so have a prolonged residence time in the circulation. By the action of cholesteryl ester transfer protein, cholesteryl esters are replaced by TG in LDL and HDL particles (fig 15♠). TG rich LDL is a good substrate for hepatic lipase that finally generates small dense LDL, which is associated with increased cardiovascular risk. ***(Packard et al; 2003).***

Many studies have shown that small, dense LDL particles have proatherogenic properties such as: (a) reduced LDL receptor mediated clearance, (b) increased arterial wall retention, (c) increased susceptibility to oxidation ***(Chait et al; 1993).***

The heterogeneity of LDL is based on the variable content of the cholesteryl ester molecules in the core of LDL, while the absolute amount of apo B on the surface of LDL may remain unchanged ***(Kwiterovich et al; 2002).***

As a result, the LDL particles are not only small and dense but also comparatively enriched in apo B molecule compared with normal LDL. In the increased TG state, small dense LDL with hyperapolipoprotein B is more likely to be formed ***(Kwiterovich et al; 2002).***

In the Johns Hopkins coronary artery disease study, higher apo B levels predicted coronary heart disease better than did LDL cholesterol ***(Kwiterovich et al; 1992).***

Hyperapobetalipoproteinaemia was the most prevalent lipoprotein phenotype in the Johns Hopkins coronary artery disease study population and was found in about 33% of patients with premature coronary heart disease ***(Kwiterovich et al; 1993).***

Low HDL cholesterol:

Low HDL cholesterol in patients with the MetS is often considered as secondary to raised TGs, in the presence of increased plasma TG levels, the cholesteryl ester transfer protein mediates TG-cholesteryl ester exchange between LDL and VLDL, as already mentioned above. Similar lipid exchange is taking place between VLDL and HDL particles, forming TG rich HDL (fig 15). These TG rich but cholesterol depleted HDLs are more prone to be catabolised. They undergo hydrolysis of their TG component and dissociation of their protein component, apo A (the main protein of HDL) ***(Wilson et al; 2003).***

There are additional mechanisms that contribute to the low HDL cholesterol levels. One possibility is that changed lipid flux in the liver attributable to insulin resistance may reduce the hepatic production of apo A.[1] However, there are studies showing that the diameter of HDL is affected by insulin resistance (see section of familial combined hypercholesterolaemia). Alternatively, the insulin resistance may cause the destabilisation of ATP binding cassette A1 transporter protein, a key molecule that mediates the transfer of cellular phospholipids and

cholesterol to apo A for the formation of mature and functional HDL particles ***(Adams et al; 1985).***

Mutations in the ATP binding cassette A1 transporter are associated with Tangier disease, which is characterised by extremely low HDL cholesterol levels ***(Rust et al; 1999).***

In the absence of sufficient cholesterol efflux, apo A is rapidly cleared from the circulation by the kidneys. The consequence of that is low HDL cholesterol in plasma, whose pleiotropic (antioxidant, anti-inflammatory, and other) effects besides the reverse cholesterol transport, have been recently established ***(Kolovan et al; 2002.)***

Furthermore, the increase of HDL cholesterol levels with lipid lowering drugs has been shown to be beneficial ***(Kolovan et al; 2003 , Robins et al; 2001).***

Another possibility is that people with the MetS, even with normal fasting TG levels, have frequently abnormal postprandial responses to dietary fat. This transient increase of TGs increases cholesteryl ester transfer protein mediated lipid exchange and formation of HDL particles, as described above ***(Taira et al; 1999).***

Postprandial lipaemia

Under conditions of insulin resistance, the antilipolytic effect of insulin on adipose tissue is weak ***(Rebuffee-Scrive et al; 1987).***

This can explain the raised free fatty acid levels seen postprandially. There is a progressive increase in plasma free fatty acid levels, which results in an eight hour plasma free fatty acid concentration that remains above fasting levels ***(Couillard et al; 1998).***

Additionally, insulin resistance has two potential effects on chylomicron remnant metabolism, the main lipoprotein formed postprandially. Firstly, it downregulates LDL receptor expression, and secondly, it increases hepatic cholesterol synthesis and VLDL secretion ***(Cummings et al; 1995).***

These effects increase competition between chylomicron and VLDL remnants for hepatic receptors, thereby impairing the uptake of chylomicron remnants by this pathway ***(AD 1997).***

Another possible explanation is that the disturbances in TG postprandially may be related to the cholesterol homoeostasis. The hepatic cholesterol synthesis and intestinal cholesterol absorption are responsible for the cholesterol content in the liver. The increased intestinal cholesterol absorption reduces hepatic cholesterol synthesis and as a consequence the secretion of VLDL decreases and the LDL receptors are upregulated ***(Thompson et al; 1996).***

The upregulation of LDL receptors may increase the removal of both chylomicron and VLDL remnants. In the postprandial state of subjects with the MBS, the increased hepatic cholesterol synthesis and the decreased intestinal cholesterol absorption result in a non-decrease of the catabolism of TG remnants (***Patsch et al; 1992).***

Studies have shown that abnormal postprandial lipaemia is found in patients with coronary heart disease, and other conditions related to an increased risk of cardiovascular disease ***(Patsch et al; 1992, Kolavou et al; 2005).***

Type 2 Diabetes, Familial Combined Hyperlipidemia, and Metabolic Syndrome

Type 2 Diabetes & Mets:

The pathophysiology of the development of type 2 diabetes mellitus is complex, multifactorial, and develops over a protracted period of time. Resistance to the action of insulin arises first. It is believed that obesity leads to insulin resistance and increased circulating insulin concentrations over time ***(Golgstein et al; 2003).***

Hyperglycaemia occurs later, as pancreatic insulin secretion eventually fails to provide sufficient insulin for the metabolic needs of the body. It seems that at some point a loss of control of blood glucose begins to emerge, resulting in dietary glucose intolerance. This ultimately results in type 2 diabetes ***(Steinberg et al; 2003).***

It is known that obese people may develop different degrees of insulin resistance, and not all people develop glucose intolerance. The factors that make some people more likely to develop type 2 diabetes mellitus are not well understood at the present time. A strong family predisposition is known to exist. Type 2 diabetes mellitus has long been considered a disease of adults ***(Vinicor F 1994).***

During the past 10 years, however, an increasing frequency in the occurrence of type 2 diabetes mellitus has been reported in adolescents ***(Pinhas-Hamiel et al; 1996).***

The lipid and lipoprotein abnormalities seen in type 2 diabetes are similar to those found in the MBS, but more severe. The raised TG rich lipoproteins are attributable to increased availability of free fatty acids in

the liver. Raised levels of free fatty acids produce lipotoxicity, which hampers the glucose induced insulin secretion and worsens the insulin ***resistance (Boden G 1996).***

Furthermore, the increased TG causes the formation of small dense LDL particles and reduction of HDL cholesterol. Patients with diabetes mellitus have higher risk for cardiovascular events compared with those without diabetes mellitus. About 80% of deaths of patients with diabetes mellitus are caused by cardiovascular disease ***(Haffner et al; 1998).***

These data support the ATP III guidelines for treating patients with diabetes mellitus as aggressively as patients without diabetes mellitus but with myocardial infarction ***(Haffner et al; 1998).***

Familial combined hyperlipidaemia & Mets:

The metabolic abnormalities associated with the MetS are also present in patients with familial combined hyperlipidaemia. Familial combined hyperlipidaemia is characterised by a varied expression of hypertriglyceridaemia and hypercholesterolaemia ***(Ayyobi et al; 2003).***

It is a highly atherosgenic disorder affecting 1%–2% of the Western world and is found in up to 10% of patients with premature myocardial infarction. Familial combined hyperlipidaemia was originally described in families of myocardial infarction survivors by the presence of hypertriglyceridaemia, hypercholesterolaemia, or both in the affected family members as a monogenic disorder ***(Goldstein et al; 1973).***

However, the inheritance of the familial combined hyperlipidaemia associated phenotype has been shown to be complex. The three major lipoprotein abnormalities observed in the MBS (increased fasting and

postprandial TG rich lipoproteins, decreased HDL, and a shift to small, dense LDL particles, proved to contribute to the pathogenesis of atherosclerosis) are probably the same in familial combined hyperlipidaemia. Insulin resistance is often seen in patients with familial combined hyperlipidaemia and is associated with impaired suppression of lipolysis by hormone sensitive lipase in adipocytes, producing an increased flux of free fatty acids to the hepatocyte, culminating in increased synthesis of VLDL. Insulin resistance, which also diminishes lipoprotein lipase activity, as mentioned before, would amplify the extent of hypertriglyceridaemia. Obesity is seen in patients with familial combined hyperlipidaemia, independently of insulin resistance, which would further contribute to hyperlipidaemia. Increased insulin concentrations are associated with the phenotype of smaller diameter HDL particles, but not with concentrations of apo A-I or apo A-II (main proteins of HDL particle). This suggests the existence of genes, which pleiotropically influence variation in both HDL and insulin levels, contributing to the clustering of proatherogenic traits in insulin resistance states ***(Rainwater et al; 1997).***

In 2001, the third workshop on familial combined hyperlipidaemia redefined this syndrome ***(Sniderman et al; 2002).***

Hypertriglyceridaemia and small dense LDL were characterised as the underlying metabolic defects. The hypertriglyceridaemia in familial combined hyperlipidaemia can be attributed to multiple factors. Many patients present a significant reduction of lipoprotein lipase, responsible for hydrolysis of TG in chylomicrons and VLDL and others an overproduction of apo B. This overproduction of apo B cannot be explained only by the MBS phenotype but probably specific genes are involved ***(Jarvik et al; 1994).***

Additionally, patients with familial combined hyperlipidaemia also manifest increased plasma free fatty acids that accompany the delayed removal of postprandial lipoproteins ***(Jarvik et al; 1994).***

Diagnosis of Metabolic Syndrome

(I) Abdominal Obesity & Mets:

The inclusion of a measure of excess adiposity [waist circumference (WC)] as one of the ATP III criteria for diagnosing the metabolic syndrome seems incongruent as, in contrast to other criteria, it is not a consequence of insulin resistance. Instead, obesity is a lifestyle variable that, along with physical inactivity, has an adverse effect on insulin-mediated glucose disposal, thereby increasing chances that the abnormalities and clinical syndromes associated with insulin resistance will develop, **(Abbasi et al; 2002).**

Stated more specifically, insulin resistance/hyperinsulinemia does not cause obesity; obesity is a physiologic variable that increases the likelihood that an individual will be insulin resistant. To understand the metabolic syndrome in pathophysiologic terms, it is necessary that obesity be viewed as contributing to insulin resistance/hyperinsulinemia, in contrast to the other four criteria, which represent changes that are more likely to occur in insulin-resistant/hyperinsulinemic individuals, **(Abbasi et al; 2002).**.

The fact that obesity is not a consequence of insulin resistance/hyperinsulinemia should not obscure the fact that the more overweight/obese an individual, the more likely it is that the individual will be sufficiently insulin resistant to be at increased risk to develop one or more of the adverse clinical consequences associated with the defect in

insulin action. This is clearly of great clinical significance in light of the current worldwide epidemic of obesity. On the other hand, although being overweight/obese increases the chances of an individual being significantly insulin resistant, by no means are all overweight/obese individuals insulin resistant, and, of greater clinical relevance, weight loss in overweight/obese individuals who are not insulin resistant does not lead to substantial clinical benefit ***(Abbasi et al; 2002, McLaughlin et al; 2002, McLaughlin et al; 2003).***

Therefore, being overweight/obese is a finding that should alert the healthcare provider to the possibility that an individual is insulin resistant and at increased risk to develop the clinical syndromes listed in Table 12 . As such, the question then becomes one of the most effective ways to identify these individuals, ***(Abbasi et al; 2002, McLaughlin et al; 2002, McLaughlin et al; 2003).***

The ATP III has emphasized the importance of WC as the estimate of adiposity on the premise that it is an index more closely related to insulin resistance and its consequences than generalized obesity as determined by body mass index (BMI). However, its superiority as a clinical tool can be questioned. At the simplest level, the values of the two variables were highly correlated in a recent analysis of data from ~20 000 participants in the National Health and Nutrition Survey (NHANES) from 1988–1994 and 1999–2000. More specifically, the *r* values were >0.9 in every subgroup analyzed and were essentially identical irrespective of differences in sex, age, or ethnicity, ***(Ford et al; 2003).***

Height and weight are routinely measured in most healthcare facilities in a reasonably simple fashion, and the BMI is easily calculated by referring to simple tables. In contrast, the following paragraph

contains the directions for measuring WC according to the NHANES protocol: The subject stands and the examiner, positioned at the right of the subject, palpates the hip bone to locate the iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at normal minimal inspiration, ***(Wang et al; 2003).***

Furthermore, as pointed out in a recent report, it appears that studies demonstrating the relationship between increased abdominal obesity and adverse clinical consequences have relied on at least 14 different methods to quantify WC, and even the 4 most commonly used approaches yielded quite different absolute values for WC***, (Wang et al; 2003).***

This issue is further confounded by a recent report from the WHO expressing concern that because the untoward effects of obesity will vary as a function of ethnicity, it will be necessary to develop ethnicity-specific values to identify overweight/obese individuals at greatest risk ***(WHO 2004).***

Given the information discussed above, it seems counterproductive to think that it will be possible to develop specific cut points for WC, varying by ethnicity, that will be measured accurately to satisfy one of the diagnostic criteria of the ATP III version of the metabolic syndrome. When these pragmatic issues are coupled with the fact that being overweight/obese simply increases the likelihood that an individual will

be insulin resistant, it seems most sensible to simply measure height and weight, assess BMI, and know that having a BMI >25.0 kg/m^2 increases the chances that an individual will be insulin resistant in the same way as, for example, having a family history of type 2 diabetes, essential hypertension, or CVD; being of non-European ancestry; or having acanthosis nigricans. It should alert one to look for the manifestations of insulin resistance–no more, no less, ***(Wang et al; 2003).***

(II) Fasting plasma glucose concentration in Mets:

The American Diabetes Association (ADA) has introduced the category of impaired fasting glucose (IFG) to classify individuals as having prediabetes", and initially suggested that individuals with a fasting plasma glucose concentration between 110 and 125 mg/dL (6.1–6.9 mmol/L) merited that designation. Because a fasting glucose ≥126 mg/dL (7.0 mmol/L) is diagnostic of diabetes, a disease unequivocally known to increase CVD risk, it seems likely that the selection of IFG by the ATP III to aid in the diagnosis of the metabolic syndrome stemmed from the creation of this new diagnostic criterion by the ADA, ***(Report of the expert committee of Diabetes 1997).***

Although there is substantial epidemiologic evidence that the higher the plasma glucose concentration, the more likely an individual is to develop type 2 diabetes, it is not as clear that the use of IFG provides a particularly effective way to identify either the presence of insulin resistance or to predict CVD risk. Values of insulin-mediated glucose disposal are distributed continuously throughout the nondiabetic population ***(Yeni-Komshian et al;2000)***, and the results of two prospective studies suggest that the one third of the population that is

most insulin resistant is at significantly increased risk to develop one or more of the clinical syndromes listed in Table 12 ***(Facchini et al; 2001).***

When this definition of clinically significant insulin resistance was applied to a population of 490 apparently healthy individuals, only 27 (5.5%) had IFG, and 17 of these 27 (63%) were in the insulin-resistant tertile, giving a test with great specificity (327 of 337, or ~97%), but low sensitivity (17 of 163, or ~10%), ***(Tuan et al; 2003).***

The sensitivity of identifying insulin-resistant individuals can be increased essentially threefold by measuring plasma glucose concentration after an oral glucose load and using the ADA diagnostic criterion for impaired glucose tolerance [IGT = plasma glucose concentration of 140–199 mg/dL (7.8–11.0 mmol/L) 120 min after a 75-g oral challenge]. Furthermore, ~25% of those in the most insulin-resistant tertile did not have prediabetes as defined by either IFG or IGT ***(Tuan et al; 2003).***

It is apparent from these findings that the presence of IFG as initially proposed by the ADA, and adopted by the ATP III, occurs too infrequently to be very useful in the diagnosis of either insulin resistance or the metabolic syndrome. Indeed, if the goal is to identify individuals at increased risk of CVD, the results of the DECODE study strongly suggest that it would be more useful to look for IGT rather than IFG ***(DECODE Study Group 2001).***

More recently, the ADA has modified its definition of IFG and now suggests that this diagnosis be applied to individuals whose fasting plasma glucose concentration is 100–125 mg/dL (5.6–6.9 mmol/L) (***(Report of the expert committee of Diabetes 2003)***, and the ATP III has

followed suit by modifying their fasting plasma glucose criterion accordingly ***(Grundy et al; 2004).***

One reason for the ADA to lower the fasting plasma glucose concentration for the diagnosis of IFG was to capture more individuals with IGT, and Tai et al. ***(Tai et al; 2004)*** have confirmed that this was the case in the Singapore CVD Cohort Study. These authors pointed out that although the prevalence of IFG increased (from 9.5% to 32.3%) with the revised criteria, associated with an increase in the number identified at risk to develop type 2 diabetes and CVD, identifying IGT was a more effective way to accomplish that goal. In contrast, Borch-Johnsen et al. ***(Barch-Johnsen et al; 2004)***, using data from multiple countries, warned that only a relative minority of those identified with the proposed ADA modification of IFG would have IGT and that the CVD risk profile would be significantly lower than in those individuals meeting the original diagnostic criterion, ***(Tai et al; 2004, Barch-Johnsen et al; 2004).***

Finally, adoption of the newly proposed ADA definition of IFG would have adverse public health consequences, with Borch-Johnsen et al. warning that use of the proposed new definition of IFG would create "a pandemic of prediabetes." Obviously, the same concerns apply to incorporating the revised ADA criterion for IFG in the guidelines for diagnosing the metabolic syndrome, ***(Tai et al; 2004, Barch-Johnsen et al; 2004).***

In the most general sense, the higher the fasting plasma glucose concentration, the more likely an individual is to be insulin resistant and at increased risk for developing the clinical syndromes listed in Table 12 . Determining the fasting plasma glucose concentration is clearly of importance for identifying patients with type 2 diabetes and subsequently

leading to the initiation of appropriate glycemic control. On the other hand, knowledge of the fasting plasma glucose concentration does not provide a particularly useful surrogate estimate of insulin resistance, accounting for only ~5%–15% of the variance (depending on degree of adiposity) in insulin-mediated glucose disposal in the population at large ***(Kim et al; 2002).***

If the plasma glucose concentration is to be used for identifying insulin-resistant individuals with increased risk to develop CVD, it seems that measurements made after an oral glucose challenge offer the most clinical utility. In the absence of obtaining this information, neither cut point for identifying patients with the metabolic syndrome proposed by the ATP III seems to be particularly useful***, (Tuan et al; 2003, DECODE Study Group 2001, Tai et al; 2004, Barch-Johnsen et al; 2004).***

(III) Dyslipidemic components of Mets:

The dyslipidemic components of the metabolic syndrome, a high TG and a low HDL-C concentration, are the ATP III criteria linked most closely to both insulin resistance and CVD risk. For example, differences in plasma TG concentration can account for ~36% of the variation in insulin-mediated glucose disposal in the same population in which fasting plasma glucose concentration accounted for only 5%–15% of the variability. Indeed, the relationship between plasma TG concentration and insulin-mediated glucose disposal is comparable to that between fasting plasma insulin concentration and insulin action, a commonly used surrogate estimate of insulin resistance ***(Yeni-Komshian et al; 2000).***

The ability of a low HDL-C to predict CVD risk has been known for many years ***(Gorden et al; 1989),*** and although issues have been

raised concerning the role of an increase in TG concentration as an "independent" CVD risk factor ***(Hully et al; 1980),*** there is certainly evidence in support of that notion ***(Austin et al; 1998).***

Furthermore, although not cited as one of the criteria for diagnosing the metabolic syndrome, the atherogenic lipoprotein profile associated with insulin resistance also includes a decrease in LDL particle diameter (small, dense LDL) and the postprandial accumulation of TG-rich remnant lipoproteins ***(Jeppesen et al; 1995),*** and these changes have also been shown to be associated with increased CVD risk ***(Patch et al; 1992).***

Furthermore, evidence from both the Helsinki Heart Study and the VA-HIT study demonstrated that the use of gemfibrozil, an agent that decreases plasma TG and increases HDL-C concentrations, significantly decreased CVD risk ***(Rubins et al; 1999).***

Of particular interest in this context is the recent analysis of the VA-HIT data indicating that individuals who had the highest plasma insulin concentrations at baseline, and were presumably the most insulin resistant, benefited the most from gemfibrozil treatment ***(Robins et al; 2003).***

Although it is possible to question the absolute cut points proposed by the ATP III for evaluating the clinical significance of plasma TG and HDL-C measurements, there is obviously abundant information suggesting that the dyslipidemic criteria proposed by the ATP III are characteristic of insulin-resistant/hyperinsulinemic individuals, are highly predictive of CVD risk, and when the conditions are treated, lead to a decreased incidence of CVD. As such, they are quite different from either

the WC or the fasting plasma glucose concentration criteria. More importantly, they raise a fundamental question as to the clinical utility of the metabolic syndrome that every healthcare provider must face: should appropriate treatment be initiated in a patient with a high plasma TG and a low HDL-C concentration, even if they do not have prediabetes or abdominal obesity? The answer to this question begins to focus the discussion on the implications of making, or not making, a diagnosis of the metabolic syndrome as defined by the ATP III.

(VI) Blood pressure & Mets:

The most complicated relationship between insulin resistance/hyperinsulinemia, the ATP III version of the metabolic syndrome, and CVD relates to the role of essential hypertension. The problem stems from the fact that no more than 50% of patients with essential hypertension are insulin resistant ***(Zavaroni et al; 1992),*** but that it is this subset of patients who are at greatest CVD risk ***(Sheuh et al; 1992, Jeppesen et al; 2000, Jeppesen et al; 2001).***

For example, patients with essential hypertension with electrocardiograph evidence of ischemic changes are somewhat glucose intolerant and hyperinsulinemic compared with either a normotensive control group or patients with essential hypertension whose electrocardiograms are entirely normal ***(Sheuh et al; 1992).***

Not surprisingly, measurement of insulin-mediated glucose disposal demonstrated that patients with essential hypertension and ischemic electrocardiograph changes were insulin resistant and that the dyslipidemic changes associated with insulin resistance/hyperinsulinemia were present in these individuals compared with normotensive individuals

or hypertensive patients with normal electrocardiograms, ***(Sheuh et al; 1992).***

The link between the dyslipidemia present in insulin-resistant/hyperinsulinemic patients with essential hypertension and CVD is consistent with results of two reports from the Copenhagen Male Study. In the first publication, Jeppesen et al. showed that the development of CVD in individuals with a high TG and a low HDL-C concentration was independent of differences in baseline systolic or diastolic blood pressure. In contrast, the higher either systolic (P <0.001) or diastolic (P <0.03) blood pressure was at the beginning of the study, the greater the incidence of CVD in those without the dyslipidemic changes associated with insulin resistance, ***(Jeppesen et al; 2000).***

In a second study, 2906 participants in the Copenhagen Male Study were divided into three groups on the basis of their fasting plasma TG and HDL-C concentrations. Patients with hypertension whose plasma TG concentration was in the upper third of the population, associated with a plasma HDL-C concentration in the lower third, were at greatest CVD risk, whereas CVD risk was not increased in those patients who did not have the dyslipidemia characteristic of insulin resistance/hyperinsulinemia, ***(Jeppesen et al; 2001).***

The evidence summarized above provides substantial support for the view that the CVD risk associated with increases in blood pressure is significantly increased when the hemodynamic abnormality is present in insulin-resistant individuals.

Metabolism And Health Implications Of Metabolic Syndrome

The principal features of the polycystic ovarian syndrome is that visceral distribution of body fat, common in the syndrome, is of greater consequence to the metabolic effects of insulin resistance than obesity per se ***(Despress et al; 1990).***

Central obesity and insulin resistance lead to an altered lipolytic response to insulin, with impaired suppression of release of free fatty acids from adipose tissue. An increased flux of free fatty acids from central sites enters the portal circulation, increasing the availability of substrate to the liver for triglyceride production. Furthermore, women with the syndrome exhibit increased activity of hepatic lipase, an enzyme responsible for the conversion of large lipoprotein particles to smaller, more atherogenic species. This explains the findings of reduced concentrations of high density lipoprotein cholesterol and increased levels of atherogenic, small, low density lipoprotein ***(Pirwan et al; 1997).***

The combination of raised triglyceride and decreased high density lipoprotein is strongly linked with cardiovascular disease, ***(Wild R 1997).***

Discrepancies in these lipid parameters between patients with polycystic ovarian syndrome and controls matched for age and weight are evident at an early age ***(Talbott et al; 1995).***

Hence, an increased risk of cardiovascular disease due to lipid perturbances will present in early adult life. Women with polycystic ovarian syndrome also show elevated concentrations of plasminogen activator inhibitor 1, ***(Ehramann et al 1997)*** , a potent inhibitor of fibrinolysis, which have been shown to predict the occurrence of

myocardial infarction. Suppression of hyperandrogenaemia by use of gonadotrophin releasing hormone analogues has little effect on the insulin resistance or the dyslipidaemia, suggesting that the abnormal lipid profile is independent of the raised androgen concentrations ***(Dunaif A 1995).***

Important retrospective studies provide evidence of increased risk of cardiovascular disorders. A study of women thought to have polycystic ovarian syndrome who were treated with ovarian wedge resection 20-30 years earlier showed that they were four times more likely to be receiving treatment for hypertension than age and weight matched controls and seven times more likely to have a diagnosis of diabetes, ***(Dahlgreen et al; 1992).***

Studies of women undergoing coronary angiography for evaluation of chest pain found a disproportionately large number with polycystic ovaries on ultrasound scan, ***(Birdsall et al; 1997).***

Furthermore, on multiple linear regression analysis the presence of polycystic ovaries was independently associated with the severity of the coronary vascular disease. Models using triglyceride concentrations, waist to hip ratio, non-insulin dependent diabetes, and elevated blood pressure in women with polycystic ovarian syndrome indicate a 7.4-fold increased risk of myocardial infarction compared with age matched referents, (***Dahlgren et al; 1992).***

Clearly, comprehensive longitudinal studies are required if the long term implications of the syndrome for cardiovascular health are to be fully appreciated.

Current & Future Managment

Of Metabolic Syndrome

The underlying risk factors that promote development of the metabolic syndrome are overweight and obesity, physical inactivity, and an atherogenic diet. All current guidelines on the management of the individual components of the metabolic syndrome emphasize that lifestyle modification (weight loss and physical activity) is first-line therapy. ATP III introduced the concept of the metabolic syndrome into its cholesterol guidelines in an attempt to highlight the need for more intensive lifestyle therapy as a means to prevent CVD in higher-risk patients. Conference participants supported this emphasis, whereas drug therapy was considered secondary, if at all, unless otherwise indicated by current CVD prevention guidelines ***(Clinical Guidelines 1998).***

Overweight and Obesity

In 1998, an expert panel was commissioned by the NHLBI and National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) to produce evidence-based guidelines on clinical management of overweight and obesity. This panel defined overweight and obesity as body mass indexes of 25 to 29.9 kg/m^2 and ≥30 kg/m^2, respectively. Abdominal obesity, defined as a waist circumference ≥102 cm (≥40 inches) in men and ≥88 cm (≥35 inches) in women, was identified as being particularly associated with several of the components of the metabolic syndrome. For this reason, ATP III recommended that abdominal obesity be considered one of the risk factors for the metabolic syndrome. It must be remembered that individuals can have the metabolic syndrome with a lesser degree of or no abdominal obesity if 3 of the remaining

components are found. Such individuals are common in certain ethnic groups, such as Asians ***(Clinical Guidelines 1998).***

Obesity guidelines stress the need for weight reduction using behavioral change to reduce caloric intake and increase physical activity. Years of study and clinical experience have revealed several key points about weight loss and weight management. The first is that "crash diets" and "extreme diets" are seldom effective in producing long-term weight reduction. Such diets include very low-calorie diets and high-fat/low-carbohydrate diets. More effective and healthful for long-term weight loss are reduced-energy diets, consisting of a modest 500- to 1000-calorie/day reduction. A realistic goal for weight reduction is to reduce body weight by ≈7% to 10% over a period of 6 to 12 months. Long-term maintenance of weight loss is then best achieved when regular exercise is included in the weight-reduction regimen. The emphasis in behavioral change should include improvements in eating habits (eg, setting goals, planning meals, reading labels, eating regular meals, reducing portion sizes, self-monitoring, avoiding eating binges). Emphasis should be placed on the benefit of social support, stress management, and the value of a regular exercise regimen. Although knowledge and education are critical, they are insufficient, and thus professional support (eg, nutrition counseling) is often very helpful. ***(Clinical Guidelines 1998).***

Physical Inactivity

Approximately 70% of the US public can be classified as being sedentary. Regular exercise and fitness have been shown to improve several metabolic risk factors and are associated with a reduction in the risk of developing many chronic diseases. For these reasons, physical

inactivity must be considered to be an important contributor to the development of the metabolic syndrome, ***(Thompson et al; 2003).***

Current physical activity guidelines recommend practical, regular, and moderate regimens for exercise. The standard exercise recommendation is a daily minimum of 30 minutes of moderate-intensity physical activity. Increasing the level of physical activity appears to further enhance beneficial effect. Suggestions that may help to initiate and maintain a regular exercise regimen include incorporating multiple short (10- to 15-minute) bouts of activity (brisk walking), avoiding common sedentary activities in leisure time (television watching and computer games), purchasing simple exercise equipment for the home (eg, treadmills), adding regular exercise into daily schedule (eg, brisk walking, jogging, swimming, biking, golfing, team sports), and self-monitoring of exercise. More exercise (ie, 1 hour daily) is even more efficacious for weight control, ***(Thompson et al; 2003).***

Because of the relation between physical inactivity and the metabolic syndrome, management of the latter should include initiation of a program of regular physical activity. As already mentioned, physical activity is one modality associated with successful weight reduction, particularly for weight maintenance. Conference participants reviewed several clinical trials that showed that the combination of weight reduction and increased physical activity can halve progression to new-onset diabetes over a period of several years in persons with prediabetes, defined as IFG or IGT. Whether weight reduction together with regular exercise will reduce risk for CVD has not been adequately tested in controlled clinical trials; nonetheless, epidemiological data are supportive, and the favorable effects of weight reduction and exercise on CVD risk

factors provide strong support and justification for recommending them as part of a regimen to reduce risk for CVD ***(Thompson et al; 2003).***

Dietary Modification:

ATP III recommendations for diet composition for patients with metabolic syndrome are consistent with general dietary recommendations ***(US Department of Agriculture & US Department of Health Human Services 2000 , American Diabetes Association 2002).***

These guidelines call for low intake of saturated fats, *trans* fats, and cholesterol; reduced consumption of simple sugars; and increased intakes of fruits, vegetables, and whole grains. An important question is whether patients with metabolic syndrome will benefit from a shift to relatively more unsaturated fats. Very high-carbohydrate diets may accentuate atherogenic dyslipidemia, and this risk factor is reduced by isocalorically substituting a higher intake of unsaturated fats. The clinical significance of diet-induced atherogenic dyslipidemia, however, is undetermined. Recent small clinical trials indicate that improvement of atherogenic dyslipidemia by increasing unsaturated fat consumption is relatively small when compared with standard dietary recommendations ***(US Department of Agriculture & US Department of Health Human Services 2000 , Krauss et al; 2000).***

Management of Metabolic Risk Factors:

Although therapeutic lifestyle modification is first-line therapy for the metabolic syndrome and thus deserves initial attention, drug therapy may be necessary in many patients to achieve recommended goals. Risk assessment in patients with metabolic syndrome is critical for setting goals of therapy.

Risk Assessment:

In the conference on definition of metabolic syndrome, ***(Grundy et al; 2004***), investigators from the Framingham Heart Study showed that the standard Framingham risk equations, which include cigarette smoking, blood pressure, total cholesterol, HDL cholesterol, and age, capture most of the risk for CVD in patients with the metabolic syndrome. Adding abdominal obesity, triglycerides, and fasting glucose to these equations provides little or no increase in power of prediction. Whether adding other parameters that contribute to the components of the metabolic syndrome—apolipoprotein B, small LDL, CRP, fibrinogen—to these risk equations will improve prediction of coronary heart disease (CHD) risk has not been tested extensively. At present, therefore, a practical approach to estimating CHD/CVD risk in patients with the metabolic syndrome is to use the standard Framingham algorithm. The risk of developing diabetes is highly dependent on the presence of obesity and IFG—2 components of the syndrome. Whether to carry out OGTT in persons with obesity and/or IFG was debated. Obtaining the 2-hour value in an OGTT may increase the likelihood of finding that a patient already has diabetes or IGT. The presence of IGT signifies increased risk for developing diabetes. Framingham data, however, fail to show independent predictive power of IGT for CVD, although diabetes definitely raises CVD risk. Therefore, OGTT adds power only for detecting or predicting diabetes but not CVD. Moreover, oral glucose testing is inconvenient and adds cost to evaluation. Finally, persons who have diabetes only diagnosed by an OGTT will likely develop diabetes diagnosed by fasting plasma glucose in a relatively short time, and it is unclear whether the hiatus will be clinically meaningful. Therefore, OGTT is not now widely recommended as routine for obese persons who

have the metabolic syndrome but must be placed in the category of optional testing based on clinical judgment ***(Grundy et al; 2004***).

Atherogenic Dyslipidemia:

Beyond lifestyle modification, several drug alternatives may be considered in patients with atherogenic dyslipidemia. ATP III emphasized that LDL cholesterol is the primary target of lipid-lowering therapy. Statins will reduce all apolipoprotein B–containing lipoproteins and often can achieve the ATP III goals for LDL cholesterol as well as for non-HDL cholesterol. Several clinical trials have confirmed the benefit of statin therapy ***(National Cholestero; Education Program NCEP 2002).***

Fibrates improve all components of atherogenic dyslipidemia and appear to reduce the risk for CVD. Their use in combination with statins is particularly attractive. However, both fibrates and statins have the potential to produce myopathy, and when they are used together, risk for myopathy is enhanced, ***(Pasternak et al; 2002).***

The literature contains many isolated reports of severe myopathy occurring from the combination of statin plus gemfibrozil. Recent evidence further indicates that gemfibrozil interferes with catabolism of statins in the liver, which can raise statin blood levels, thereby predisposing to myopathy. Fenofibrate does not interact adversely with statin catabolism and thus may be safer to use in combination therapy. Nicotinic acid has similar features to fibrates, and the combination of nicotinic acid and statins is promising. Nicotinic acid is especially efficacious for raising HDL cholesterol levels, but higher doses can raise plasma glucose levels. Therefore, if nicotinic acid is used in patients with

IFG, IGT, or diabetes, its dose should be kept relatively low (eg, 1 to 2 g per day) ***(Pasternak et al; 2002).***

Elevated Blood Pressure:

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) introduced a new category of "prehypertension" (120 to 139/80 to 89 mm Hg), in recognition of the fact that underlying risk factors raise blood pressure to ranges that increase risk for CVD. This recognition accords with ATP III's adding of blood pressures ≥130/≥85 mg/dL to the list of risk factors comprising the metabolic syndrome. In persons with categorical hypertension (blood pressure ≥140/≥90 mm Hg), drug therapies are required according to JNC 7 recommendations. In patients with established diabetes, antihypertensive drugs should be introduced at even lower blood pressures (≥130/≥80 mm Hg). No particular antihypertensive agents have been identified as being preferable for hypertensive patients who also have the metabolic syndrome. Diuretics and ß-blockers in high doses can worsen insulin resistance and atherogenic dyslipidemia, (***Chobanian et al; 2003).***

For thiazide diuretics, doses should be kept relatively low in accord with current recommendations. ß-Blockers are cardioprotective in patients with established CHD and are no longer contraindicated in patients with type 2 diabetes. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are useful antihypertensive drugs, and some clinical trials (but not all) suggest that they carry advantages over other drugs in patients with diabetes. At this time, however, the majority of clinical trials indicate that most of the risk reduction associated with

antihypertensive drugs is the result of blood pressure lowering alone, ***Chobanian et al; 2003).***

Insulin Resistance and Hyperglycemia:

There is growing interest in the possibility that drugs that reduce insulin resistance will delay onset of type 2 diabetes and will reduce CVD risk when the metabolic syndrome is present. The Diabetes Prevention Program showed that metformin therapy in patients with prediabetes will prevent or delay the development of diabetes. Data on use of the thiazolidinedione troglitazone suggested a similar effect, but this drug has been withdrawn from commercial use. Although insulin resistance is associated with increased CVD risk, neither metformin nor any of the thiazolidinediones now on the market have been shown to reduce the risk of CVD in those with the metabolic syndrome, prediabetes, or diabetes. Thus, there is insufficient evidence to recommend these drugs for anything other than their glucose-lowering action, ***Chobanian et al; 2003).***

The presence of the metabolic syndrome in patients with type 2 diabetes conveys a particularly high risk for CVD. When both are present, appropriate treatment of dyslipidemia and hypertension is essential. Good glycemic control is also important because of the evidence suggesting that a reduction in A1C level to 7.0% or less will reduce CVD events. Choice of drug therapy beyond lifestyle changes to achieve this glycemic goal depends on clinical judgment (***Chobanian et al; 2003).***

Prothrombotic State:

A prothrombotic state in patients with the metabolic syndrome is characterized by elevations of fibrinogen, PAI-1, and possibly other

coagulation factors. However, these are not measured routinely in clinical practice. The risk for thrombotic events can be reduced by aspirin therapy. The AHA currently recommends use of aspirin prophylaxis in most patients whose 10-year risk for CHD is ≥10% as determined by Framingham risk scoring. Including patients with metabolic syndrome when their 10-year risk for CHD is ≥10% is appropriate, ***(Pearson et al; 2002).***

Pro-inflammatory State:

This condition is characterized by elevated cytokines (eg, tumor necrosis factor-α and interleukin-6) as well as by elevations in acute-phase reactants (CRP and fibrinogen). Measurement of CRP is the most practical way to assess the presence of an inflammatory state. CRP levels tend to be higher than normal in patients with the metabolic syndrome. An elevated CRP (≥3 mg/L) is an emerging risk factor for CVD ***(National Cholesterol Education Program NCEP 2002).***

The AHA and Centers for Disease Control and Prevention (CDC) recently issued guidelines for measurement of CRP in clinical practice. They suggested that such measurements can be made at the physician's discretion, but testing should be limited to individuals assessed to be at intermediate risk by Framingham scoring, ie, those whose 10-year risk for CHD is in the range of 10% to 20%. The purpose of CRP testing in an intermediate-risk patient is to find those with high CRP levels whose risk category should be raised to high. The practical consequences of elevating the risk category would be to intensify lifestyle therapies, make certain that low-dose aspirin is used, and set lower LDL goals ***(Pearson et al; 2003).***

AIM OF THE PRESENT STUDY

The aim of the present study was to:

- Determine insulin sensitivity by early detection of insulin resistance.
- To find out the prevalence of Metabolic Syndrome (MBS) amoung patients with Polycystic ovary syndrome, both obese and non obese.
- To detect the relation between insulin resistance and Metabolic Syndrome.

SUBJECTS & METHODS

This is a cross sectionalstudy done in the period from 12/2004 until 2/2007. This controlled clinical study was carried out on 160 selected women.

An informed consent was taken from each case included in this study.

Inclusion Criteria:

- Not known to be diabetic, hypertensive, cardiac, or suffering from any metabolic disorders,
- None of the subjects have been taking any drug known to affect carbohydrate metabolism, for at least 3 months prior to endocrinal and metabolic investigations.
- The age of all cases was ranging between 19 & 35 years.

Exclusion Criteria:

- Women who were having only positive ultrasonic diagnosis of PCOS with no other hormonal abnormality or menstrual irregularities were excluded from the currunt study

Cases were divided into two groups:

I . Study Group: This group included 80 patients with PCOS.

**** Diagnosis of PCOS accorrding to:***

- Ultrasonographic diagnosis of Polycystic ovaries.
- Elevated Free Serum Testosterone,(hyperandrogenism).
- History of disturbed menstrual cycle, and symptoms indicating chronic anovulation.

This study group was divided into two sub-groups, obese and non-obese according to the Body mass index;

*** Study Group "A" :** Included 40 PCOS Obese patients, i.e. BMI ≥ 30 *(Accorrding to the National index)*.

*** Study Group "B"** : Included 40 PCOS non-obese patients, i.e. BMI ≤ 30, *(Accorrding to the National index)* .

II. Control Group : This group included 80 patients with regular menstrual cycles, and no signs or symptoms of hyperandrogenisem, and normal ovarian ultrasonographic pictures (i.e. No evidence of PCO).

This control group was divided into two sub groups, obese and non-obese according to the BMI;

*** Control group "A" :** This group included 40 normal obese patients . i.e. BMI ≥ 30 , *(Accorrding to the National index)*.

*** Control group "B":** This group included 40 normal non-obese patients, i.e. BMI ≤ 30, *(Accorrding to the National index)* .

Parameters of the Study

For each case included in this study the following were carried out:

I. Clinical Evaluation:

- Detailed history taking with especial concern to menstrual history.
- General examination with especial attention to Blood pressure.
  ●Measurement of Blood Pressure : Patient was allowed to rest for 5 minutes in a seated position & the right arm was used in measurements. Cuff was applied 20 mm above the bend of the elbow and the arm parallel to the floor. The cuff was inflated up to 30 mmHg above the disappearance of brachial pulse, cuff was deflated slowly. Two measurements were obtained with two minutes rest in between, and the mean of the two blood pressure readings was taken ***(Speroff 1999).***
- Abdominal and Local examination were done.
- Signs and symptoms of hyperandrogenism were evaluated.

II. Anthropometric Variables:

This included measurement of Body weight, Height, Waist circumference, and Hip circumference.

1. BMI was calculated as Weight in kg divided by squared height in m2.

2. Measurements of the Waist circumference were taken at the narrowest point or at the level of the umbilicus, Hip circumference was measured at the level of the greater trochanter. Obese and non-obese patient were defined by the BMI, (Obese → BMI > or = 30 kg/m2 , Non-obese → BMI < or = 30 kg/m2) This is according to the "National Index".

III. Biochemical Evaluation:

Hormonal and metabolic assessment were carried out after fasting Overnight, (12 to 14 hours, from 8pm → 8am). Samples were taken for:

1. SERUM FSH & LH: Samples were taken during the follicular phase (day 2 – 3 of the menstrual cycle). Serum FSH and LH were measured by specific Immunofluroimetric assay. Results were reported in mIu/ml, with normal limits 5 – 20 mIu/ml, and 5 – 25 mIu/ml for FSH & LH respectively, (***Wallac-Turku).***

2. SERUM FREE TESTOSTERONE : Test was done by radioimmunoassay, results were reported in ng/ml. Hyperandrogenisem is defined by Serum testosterone > 1ng/dl, commercial kits were used (DPC, Los Angeles, CA, USA), (***Reaven et al 1995).***

3. FASTING SERUM INSULIN: Results were expressed in µU/ml, measurement was done by double antibody Radioimmunoassay using commercial kits. Hyperinsulinemia is defined at serum Insulin ≥ 20 µU/ml, (***Kauffman et al 2002).***

4. ORALL GLUCOSE TOLERANCE TEST (OGTT): Results were expressed in mg/dl, measurements were done by Glucose Oxidase technique using Mega Merk Kits (Darmstadt, Germany). Fasting glucose level is measured, followed by oral intake of 100 gm glucose, then re-measuring of the serum blood glucose after one, two, & three hours post-prandial. Hyperglycemia is defined at Fasting Serum

Glucose > 110 mg/dl, and two hours post-prandial > 140 mg/dl, ***(Legro et al 2002).***

5. GLUCOSE INSULIN RATIO "G/I": Ratio were calculated. Insulin resistance is defined by G/I ≤ 7.2, ***(Kauffman et al 2002).***

6. TRIGLYCERIDES: Calorimetry technique were used, results were expressed in mg/dl. The threshold value to define Hyperlipidemia is ≥ 150 mg/dl, (Fasting for 12 hours), ***(Legro et al 2002).***

7. **HIGH DENSITY LIPOPROTEIN (HDL):** Results were expressed in mg/dl using calorimetry technique, Human Kits- Germany were used . The thresh-hold value of Hyperlipidemia is at < 50 mg/dl, (Fasting for 12 hours), ***(Legro et al 2002).***

IV. Ultrasonographic Parameters:

- Transvaginal ultrasound examination was carried out for diagnosis and in the presence of PCO, Vaginal probe 5.5 MHz was used.
- Ultrasonographic signs considered for diagnosis of PCO were as follows: Enlarged ovaries with ovarian volume > 7 cm3, Ovarian volume was calculated by D1 x D2 x D3. Ovaries with multiple follicles (eight or moreabout 10mm or less in diameter) scattered either around or through an echodense thickened central stroma, ***(Adam`s et al 1986)***

V. Screening of Metabolic Syndrome (Mets):

All cases of this study were screened for the presence or absence of "Metabolic Syndrome", according to the following criteria:

RISK FACTOR	CUTOFF
1. Abdominal Circumference.	> 88 cm (35 inch)
2. Serum Triglycerides.	≥ 150 mg/dl
3. Serum High Density Lipoprotein in women.	< 50 mg/dl
4. Systolic blood pressure	≥ 130 mm Hg
Diastolic blood pressure.	≥ 85 mmHg
5. Fasting Blood Glucose	110 – 126 mg/dl
2-hours Glucose from oral glucose tolerance test	140 – 199 mg/dl

** Metabolic syndrome is considered to be present when the participant met at least three out of the above mentioned criteria, (***Revean 1988)*.

Statistical Analysis

The results of this study were analysed to find out the relationship between insulin sensitivity, and the incidence of Metabolic syndrome amoung women with PCOS.

All data and figures in this study were presented as mean ± Standard deviation (SD). Relationships between variables were calculated by using correlation analysis (Spearman`s rank correlation coefficient). The threshold for statistical significance were at the P value($P < 0.05$ was considered statistically significant).

Comparison of the different variables were done between PCOS women group (obese & non-obese), and Non-PCOS group= Control group (obese & non-obese).

RESULTS; Hormonal parameters

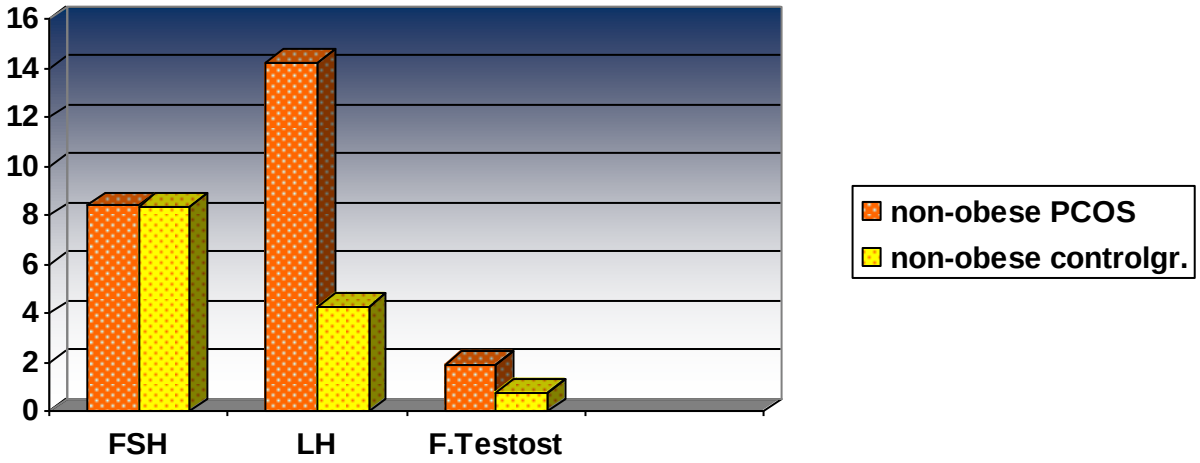
As shown in Table "6" serum LH & Free Testosterone were significantly high (P = 0.002 & 0.007 respectively), amoung non-obese PCOS patients both compared to non-obese control subjects, Level of serum FSH shows no significance (P = 0.04), these results are presented in Table 6, & Figure 11.

Table " 6 ": ***Hormonal parameters between non-obeses PCOS &non-obese control subjects. Data are shown as Mean ± S D.***

	Control group Non-obese N=40	PCOS Group Non-obese N=40	P Value	Significance
LH (IU/I)	4.3 ± 1.5	14.2 ± 5.2	0.002	HS
FSH (IU/I)	8.4 ± 4.3	8.5 ± 2.9	> 0.05	NS
Free Serum Testosterone ng/dl).	0.8 ± 0.8	1.9 ± 2	0.007	HS

**** Comparisons were done using T test test for independent samples (P < 0.05 = S)***

Figure "11":Comparison of Serum FSH, LH, & Free Testosterone between non-obese PCOS patients & non-obese Control group



As shown in table "7" Serum LH & Free Testosterone were significantly high (P = 0.003 & 0.001 respectively), among obese PCOS patients both compared to obese control subjects, Level of serum FSH shows no statistical difference (P = 0.06), these results are presented in Table 7, & Figure 12.

Table " 7 ": ***Hormonal parameters between obese PCOS & obese control subjects. Data are shown as Mean ± S D.***

	Control group obese N=40	PCOS Group obese N=40	P Value	Significance
LH (IU/I)	4.9 ± 2.2	11.3 ±3.5	0.003	S
FSH (IU/I)	9.2 ± 3.4	7.7 ± 2.3	0.06	NS
Free Serum Testosterone ng/dl).	0.7 ± 0.6	4.8 ± 2.5	0.001	S

**** Comparisons were done using T test test for independent samples (P < 0.05 = S)***

Figure "12":Comparison of Serum FSH, LH, & Free Testosterone between obese PCOS patients & obese Control group

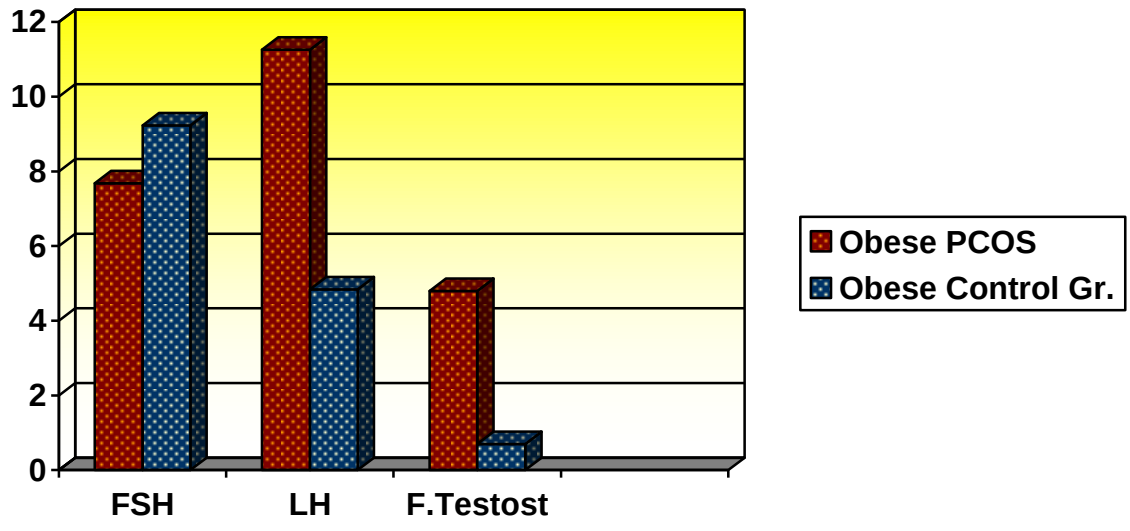
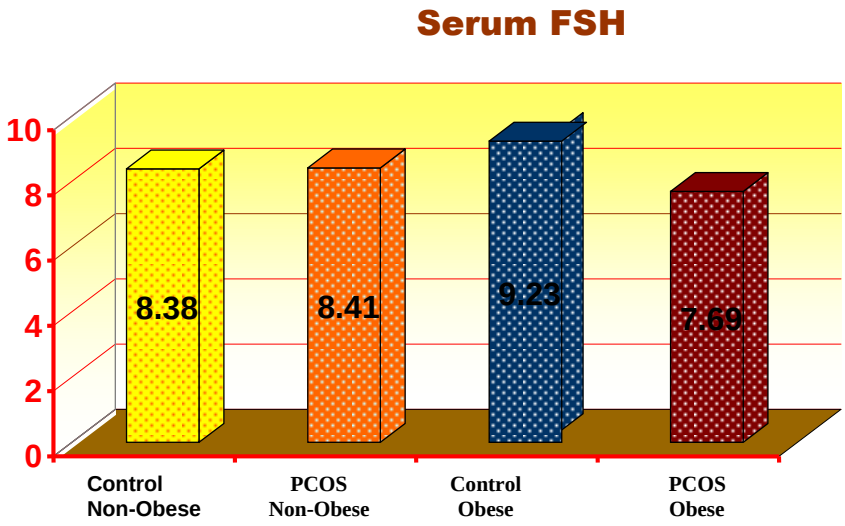
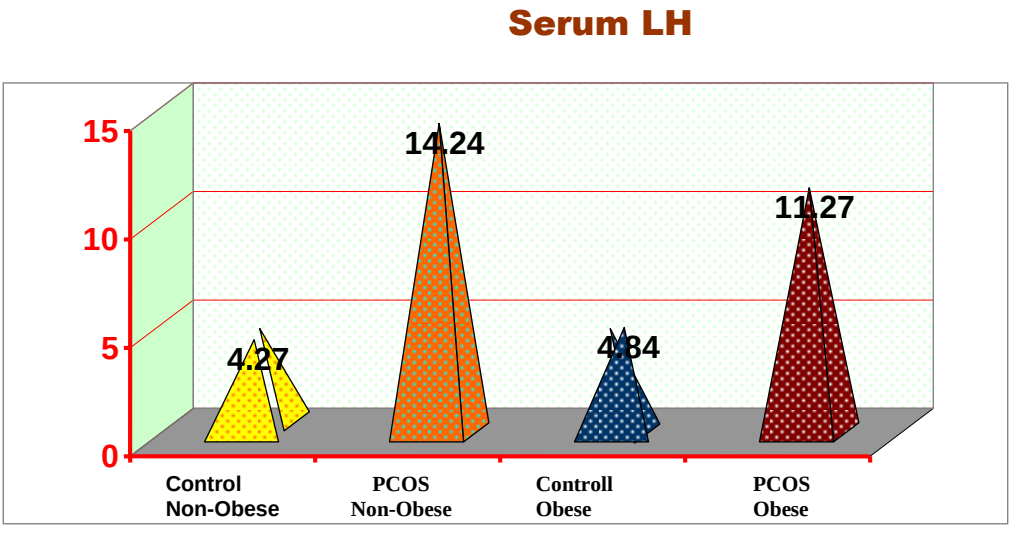


Figure "13": Comparison of Serum FSH between the four groups of the present study.



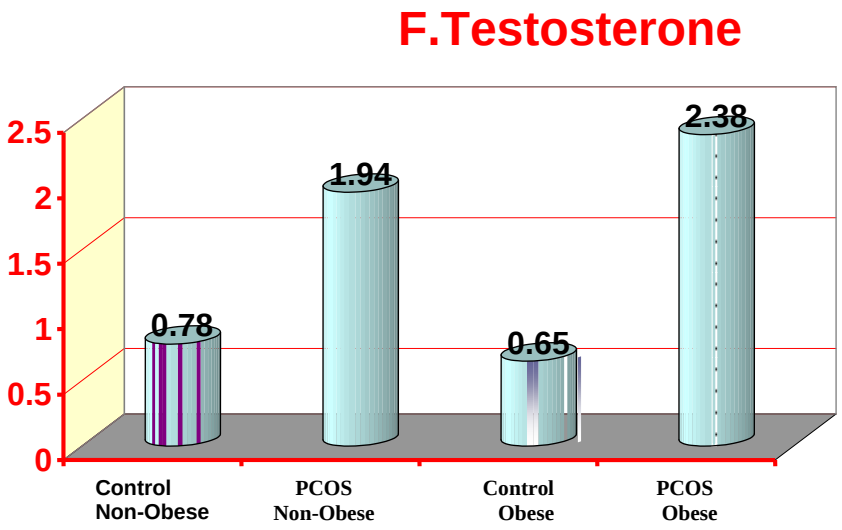
By comparing the level of Serum FSH among the four groups , there were no significant difference in between them. (P = 0.168), ***(Test used for comparison is Anova test P > 0.05*** = NS***).***

Figure "14': Comparison of Serum LH between the four groups of the present study.



By comparing the level of Serum LH among the four groups , there were significant difference in between them (P = 0.001). ***(Test used for comparison is Anova test P < 0.05 = S).***

Figure "15": ***Comparison of Free Serum Testosterone between the four groups of the present study.***



By comparing the level of Serum LH among the four groups , there were significant difference in between them, (P = 0.001). ***(Test used for comparison is Anova test P < 0.05 = S).***

Metabolic parameters

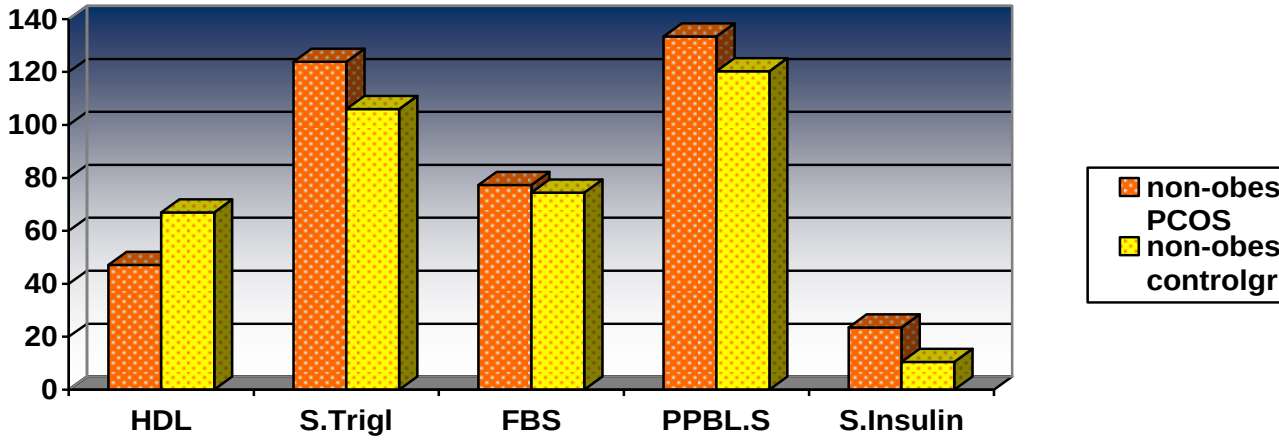
Regarding the metabolic parameters results among non-obese PCOS women revealed raised serum levels of triglyceride, reduced HDL cholesterol levels , and elevated Post-prandial blood sugar compared with non-obese control group. Results were statistically highly significant (P < 0.05) , As regard fasting blood sugar there were no stastical difference (P > 0.05), Results are presented in Table 8 & Fig 16.

Table " 8": ***Metabolic parameters, & Insulin Resistance in Non-obese PCOS & Non-obese control subjects. Data are shown as Mean ± S D.***

	Control Group Non-obese N=40	PCOS Group Non-obese N=40	P Value	Significance
Triglycrides (mg/dl)	106 ± 27	123.9±33.4	< 0 .05	S
HDL (mg/dl)	66.9 ± 16.6	47.1±18.7	< 0 .05	S
FBS (mg/dl)	74.4 ± 8.7	77.3±10.0	>0.05	NS
PPBL S (mg/dl)	120.3 ± 14.1	133.4±18.7	< 0 .05	S
Serum Insulin	10.5 ± 4.9	23.5±16.0	< 0 .05	S
Glucose : Insulin	8.0 ± 4.6	4.6±2.6	< 0 .05	S

**** Comparisons were done using T test test & Mann-Whitney test for independent samples (P < 0.05 = S)***

Figure " 16": ***Comparison of HDL, Serum Triglcerides. Fasting Blood sugar, & Postprandial blood sugar, and Fasting Serum Insulin in between non-obese Control and non-obese PCOS subjects.***



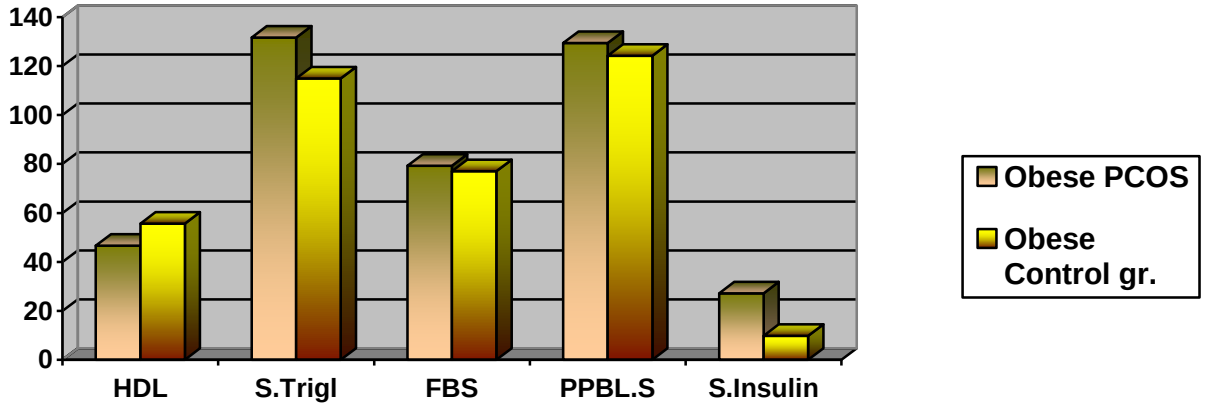
Regarding the metabolic parameters results among obese PCOS women revealed raised serum levels of triglyceride, reduced HDL cholesterol levels , and serum insulin compared with obese control group. Results were statistically significant (P = < 0 .05) . However results of fasting blood sugar & Post-prandial blood sugar were statistically not significant (P = > 0 .05) Results are presented in Table "9" & Fig 17.

Table " 9": ***Metabolic parameters, & Insulin Resistance in obese PCOS & obese control subjects. Data are shown as Mean ± S D.***

	Control Group Obese N=40	PCOS Group Obese N=40	P Value	Significance
Triglycrides (mg/dl)	114.9 ± 32.8	131.7 ± 32.3	< 0 .05	S
HDL (mg/dl)	55.7 ± 15.6	46.7 ± 16.6	< 0.05	S
FBS (mg/dl)	77.1 ±11.8	79.3 ± 11.6	> 0.05	N S
PPBL S (mg/dl)	124.2 ± 22.7	129.4 ± 15.7	< 0.05	S
Serum Insulin (µU/ml)	9.8 ± 5.3	27.1 ± 21.1	< 0.05	S
Glucose : Insulin	9.4 ± 5.1	5.9 ± 4.5	< 0.05	S

**** Comparisons were done using T test test & Mann-Whitney test for independent samples (P < 0.05 = S)***

Figure " 17": ***Comparison of HDL, Serum Triglcerides. Fasting Blood sugar, & Postprandial blood sugar, and Fasting Serum Insulin in between obese PCOS and obese Control subjects.***



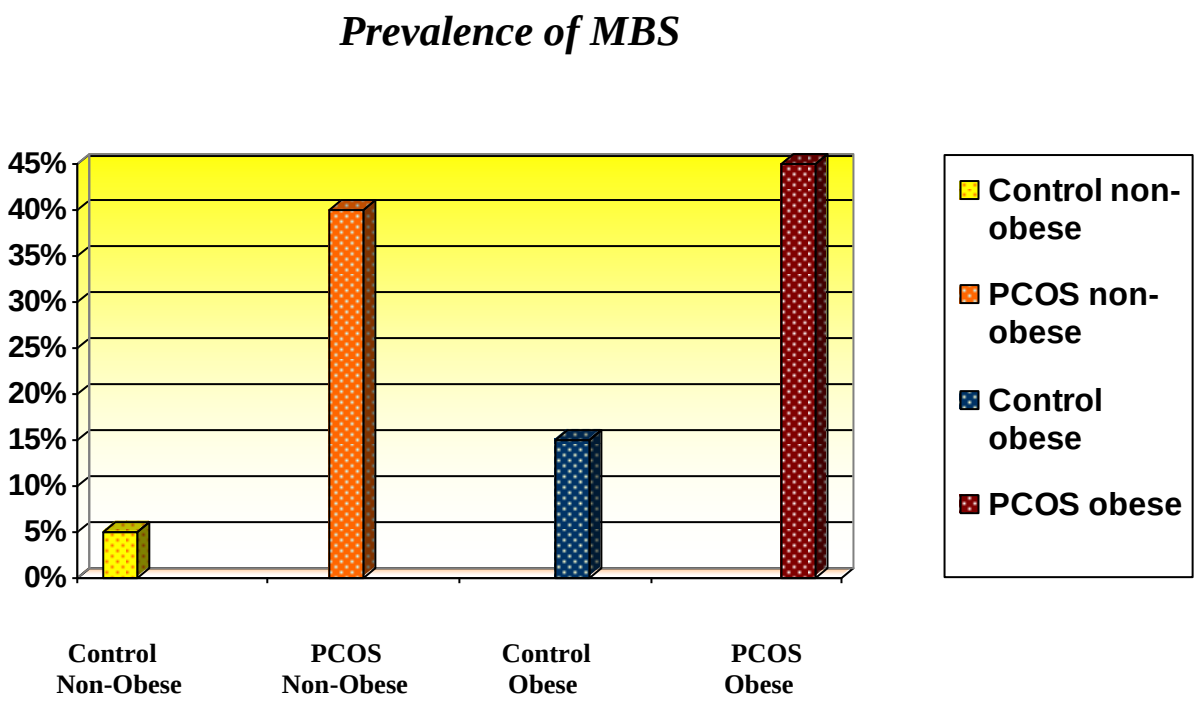
Prevelance of Metabolic Syndrome (MBS) Risk factors

Prevalence of MBS within Obese & Non-obese PCOS patients was 45% & 40 % respectively, occurring in 17 patients out of 40 , and 16 patients out of 40 subjects respectively. This is nearly three folds higher than that reported for age matched control group being 15% & 5 % respectively. These results were with significant statistical difference (*P* = 0.001).

TABLE "10 ": ***Prevalence of MBS amoung women with PCOS and Control group:***

	Prevalence (%)	No of patients
Obese PCOS Group	(17 patients) 45%	40
Non-obese PCOS Group	(16 patients) 40%	40
Obese Control Group	(6 patients) 15 %	40
Non-obese Control Group	(2 patients) 5 %	40

Figure "18" Prevalence of MBS in women with PCOS and Control group, both obese and non-obese.



After detecting the prevalence of MBS amoung all subjects included in the study, we examined the prevalence of each component of metabolic syndrome between women with PCOS, & control group both obese and non-obese.

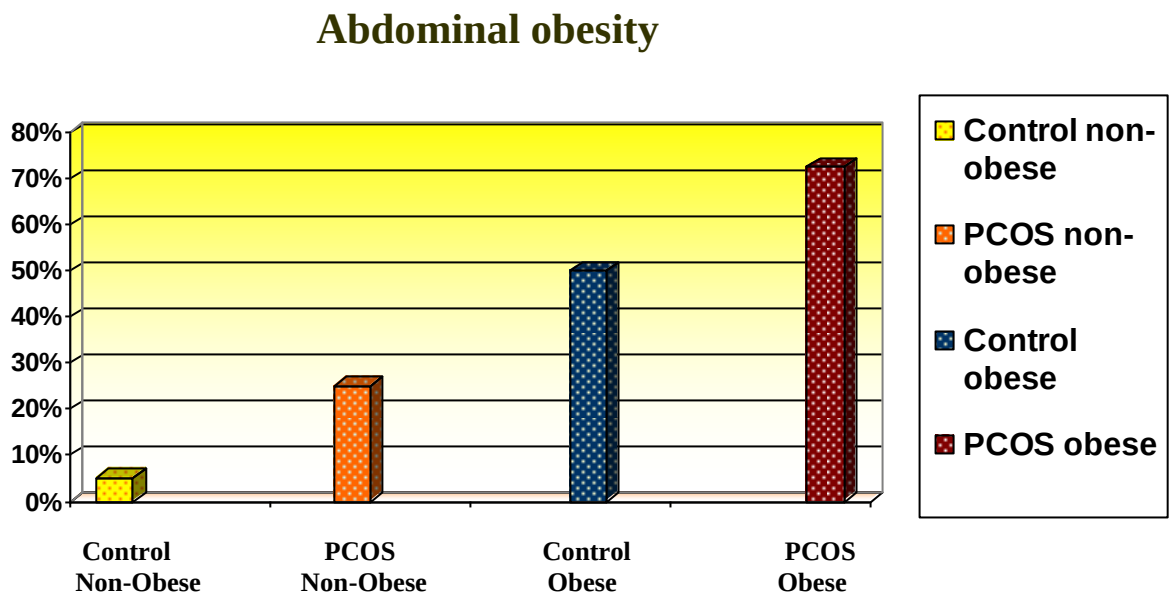
The most common abnormality in the PCOS group was abdominal obesity mainly among obese PCOS patients being 72.5 % & 25 % compared to 50% & 5% among control groups both obese & non obese respectively. These results are showed in Table 11 & fig "19".

TABLE "11" ***Prevalence of individual metabolic abnormalities among patients with PCOS & Control group both obese and non-obese:***

	PCOS Obese N=40	**PCOS Non-obese N=40**	**Control Obese N=40**	**Control Non-obese N=40**	**P value**	**Sig**
Abdominal Circum. [AC > 88 cm]	(29 patients) 72.5 %	(10 patients) 25 %	(20 patients) 50 %	(2 patients) 5 %	--	--
Hypertriglycerid [Triglyc ≥ 150mg/dl]	(16 patients) 37.5 %	(14 patients) 35 %	(8 patients) 20 %	(3 patients) 7.5 %	< 0.05	S
Low HDL [HDL < 50 mg/dl]	(24 patients) 60 %	(25 patients) 62.5 %	(12 patients) 30 %	(5 patients) 12.5 %	< 0.05	S
High blood pressure [≥ 130/85 mmhg]	(14 patients) 32.5 %	(13 patients) 32.5 %	(8 patients) 20 %	(4 patients) 10 %	< 0.05	S
High fasting glucose [> 110 mg/dl]	(9 patients) 22.5 %	(13 patients) 32.5 %	(6 patients) 15 %	(3 patients) 7.5 %	< 0.05	S

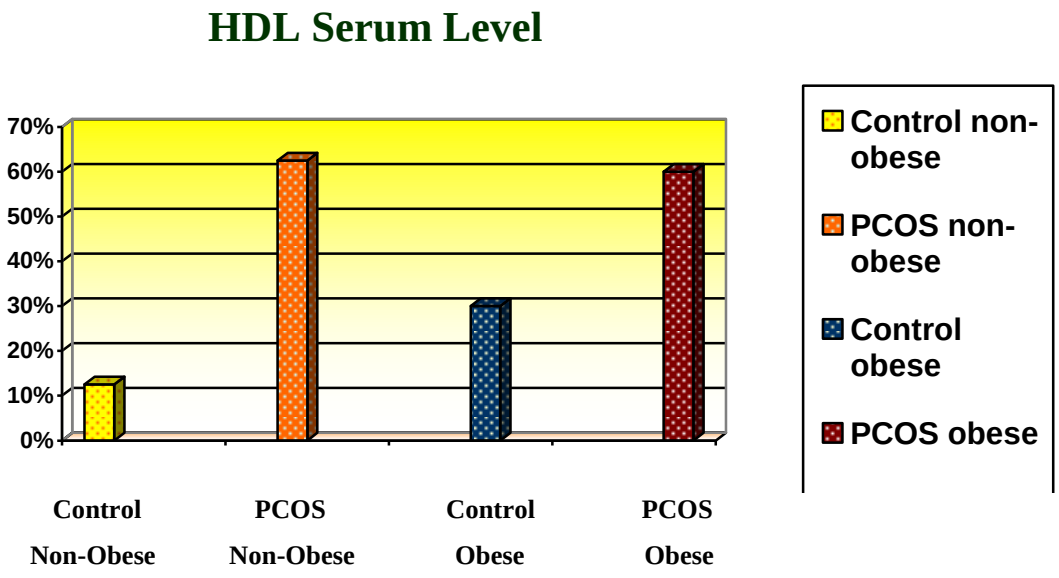
**** Comparisons were done using Chi squared test test for independent samples (P < 0.05 = S)***

Figure " 19": ***Comparison in between the four groups included in this study, (Control, and PCOS subject Both Obese & Non-obese), regarding prevelance of Abdominal obesity.***



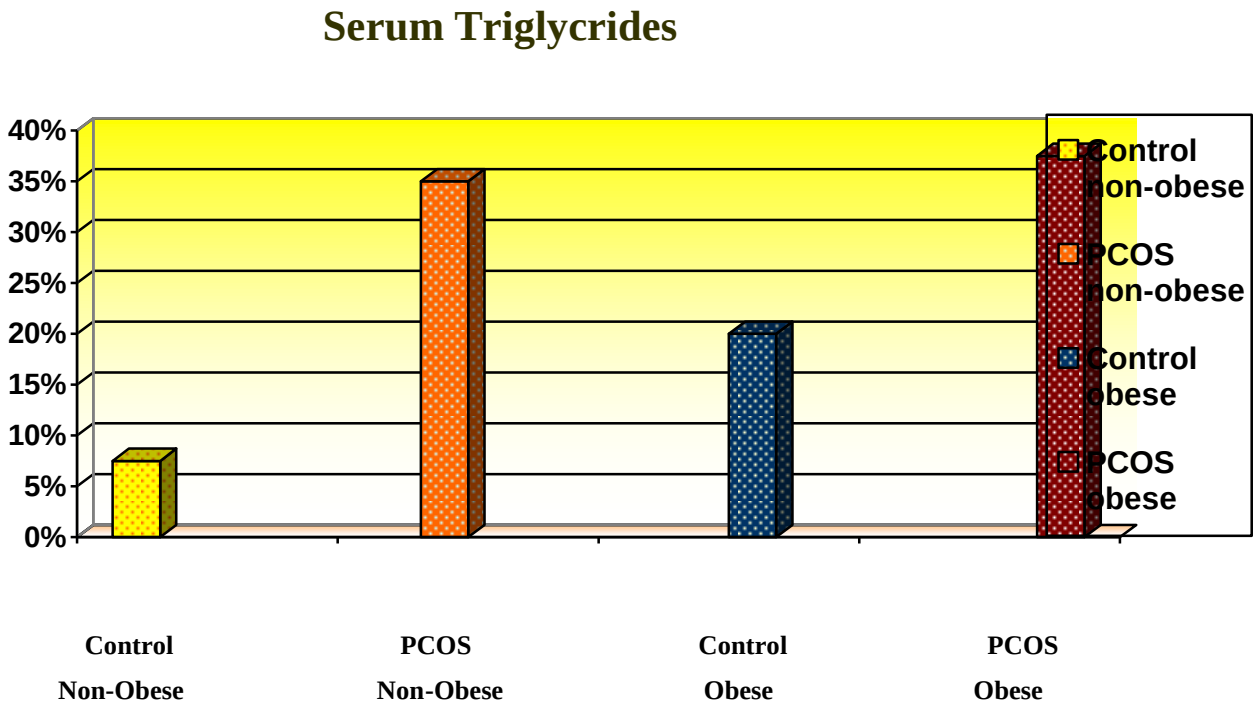
The second common metabolic abnormality is low HDL which was 60% & 62.5% amoung PCOS patients obese & non-obese respectively , compared to 30% & 12.5% amoung control group, these results is shown in table "11"& Fig "20".

Figure "20": ***Comparison in between the four groups included in this study, (Control, and PCOS subject Both Non-obese & Obese), regardingn of patients with Low serum HDL level (i.e < 50 mg/dl).***



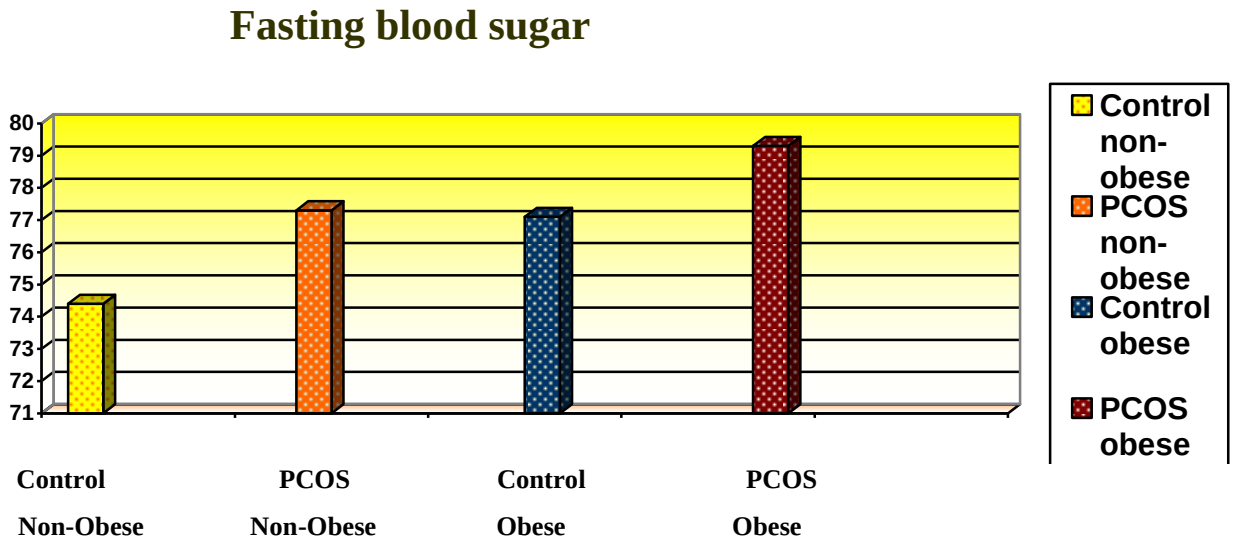
Regarding Serum Triglycerides results were higher among PCOS patients being 37.5 % & 35.5 % compared to control groups being 20 % & 7.5 % (obese & non-obese respectively),. These results are shown in table 11 & fig 21.

Figure " 21": ***Comparison of between the four groups, (Control, and PCOS subjects Both Obese & Non-obes) , as regard no. of patients with Elevated Serum Triglycrides (ie > 150 mg/dl)***



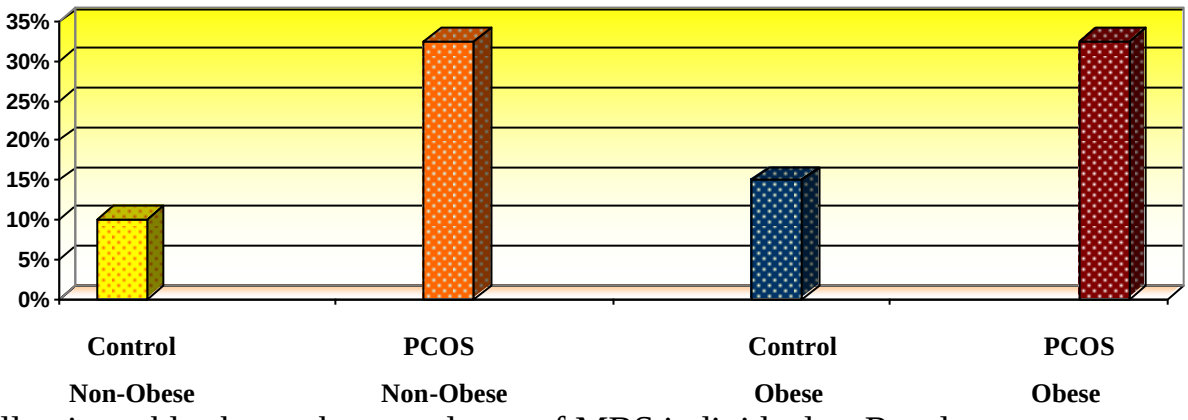
Elevated fasting glucose bl sugar was detected the least frequent in between patients with PCOS being 22.5 % & 32.5 % compared to our control group which was 15 % & 7.5 % obese & non-obese respectively, results is shown in table "11"& Fig "22".

Figure " 22 ": ***Comparison between the four groups (Control and PCOS patients Both Obese & Non-obese) as regard no of patients with high Fasting blood sugar.***



High Blood pressure showed significant difference in between patients with PCOS being 32.5 % & 32.5 % compared to our control group which was 20 % & 10 % obese & non-obese respectively, results is shown in table "11"& Fig "23".

Figure " 23":Comparison between the four groups, Control &PCOS patient (both obese & Non-obese), as regard no of patients with Elevated blood pressure.



The following table shows the prevalence of MBS individuales, Results revealed that 90 % of PCOS patients had at least one abnormality of MBS

criteria, 77.5 % had two or more abnormality compared to 77.5 % & 20 % among control group both obese and non-obese.

TABLE 12" :. Prevalence of one or more abnormalities of the Mets among patients with PCOS , control group included in the present study:

Mets factors (n)	PCOS Obese N=40	PCOS Non-obese Group N=40	Control Obese Group N=40	Control Non-obese Group N=40
0	(4) 10 %	(9) 22.5 %	(9) 22.5 %	(32) 80 %
1	(36) 90 %	(31) 77.5 %	(31) 77.5 %	(8) 20 %
2	(20) 52.5 %	(22) 55 %	(18) 45 %	(4) 10 %
3	(17) 45 %	(15) 40 %	(4) 10 %	(2) 5 %
4	(8) 20 %	(5) 12.5 %	(3) 7.5 %	(0) 0 %
5	(4) 10 %	(2) 5 %	(0) 0 %	(0) 0 %

We also comparison done obese POCS patients , and non-obese PCOS patients, (Comparisons were done using Chi squared test for independent samples), as regard the prevalence of metabolic syndrome, low HDL levels, High triglycerides, High Blood pressure, and prevalence of insulin resistance. Results revealed no significant difference in between the two groups.

Prevelance of Insulin Resistance

Prevelance of Insulin resistance was significantly higher among non-obese PCOS patients being 55 %, compared to non-obese control group being 5 %, difference was statistically highly significant (P= 0.001), results are shown in " Table 13 & fig 24".

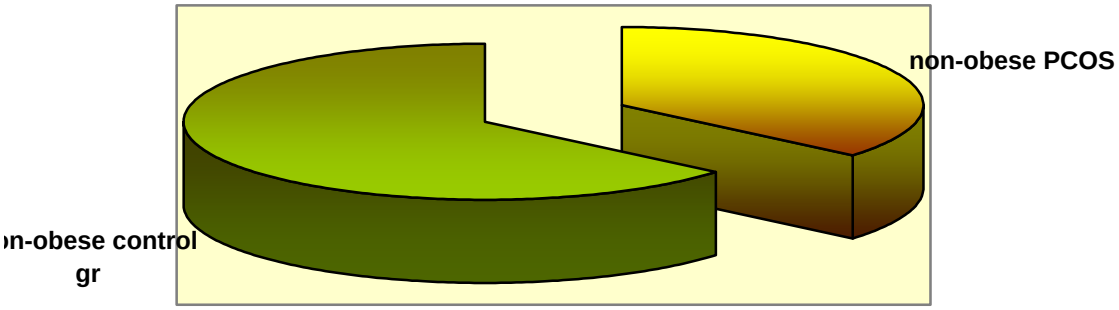
TABLE 13:. Prevalence of Insulin resistance among patients with PCOS , control group included in the present study:

	PCOS ObeseN=40	**PCOS Non-obese N=40**	**Control Obese N=40**	**Control Non-obeseN=40**	**P value**	**Sig**
Glucose : Insulin (≥ 7.5)	**(21) 52.5 %**	**(22) 55 %**	**(3) 7.5 %**	**(2) 5 %**	***< 0.05***	**S**

**** Comparisons were done using Chi squared test test for independent samples (P < 0.05 = S)***

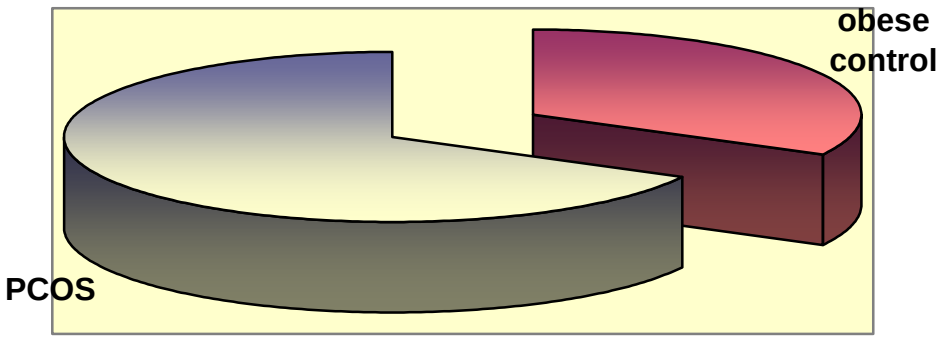
Prevelance of Insulin Resistance was significantly higher among non-obese PCOS patients being 55 %, compared to non-obese control group being 5 % , difference was statistically highly significant (***P < 0.05 = S)***, results are shown in " Table 13 & fig 24".

Figure " 24": ***Comparison of G/I (≤ 7.2)in between non-obese Control and non-obese PCOS subjects.***



Prevelance of Insulin Resistance was also significantly higher among obese PCOS patients being 52.5 %, compared to obese control group being 7.5 % , difference was statistically highly significant (comparison done usig Chi Squared test P < 0.05), results are shown in " Table 13 & fig 25".

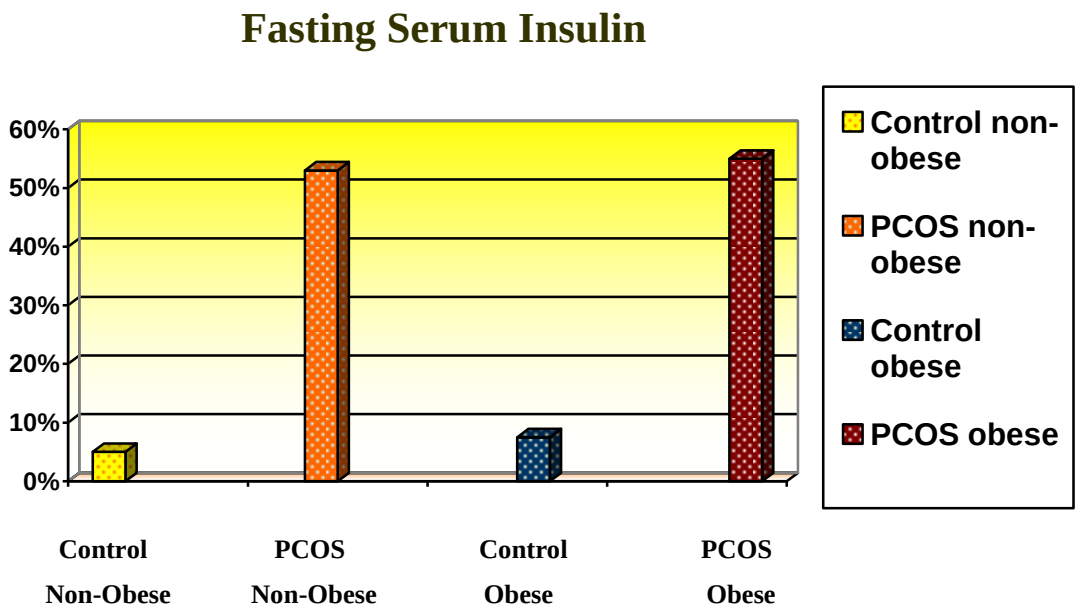
Figure " 25": ***Comparison of G/I (≤ 7.2) in between obese Control and obese PCOS subjects.***



As regard prevalence of Hyperinsulinemia (Serum Insulin level ≥ 20 µU/ml) . Results revealed high prevalence among patients with PCOS , being 50 % & 55 % Both obese and non0obese, compared to 8 % & 5 %

among control group both obese and non-obese, results are shown in figure “23”.

Figure “26”: ***Comparison between the four groups (Both Non-obese & Obese Control, and PCOS subjects) as regard prevalence of hyperinsulinemia(High S. Insulin level..***



DISCUSSION

Since the 1990 National Institutes of Health-sponsored conference on polycystic ovary syndrome (PCOS), it has become appreciated that the syndrome encompasses a broader spectrum of signs and symptoms of ovarian dysfunction than those defined by the original diagnostic criteria. The 2003 Rotterdam consensus workshop concluded that PCOS is a syndrome of ovarian dysfunction along with the cardinal features hyperandrogenism and polycystic ovary (PCO) morphology. PCOS remains a syndrome, and as such no single diagnostic criterion (such as hyperandrogenism or PCO) is sufficient for clinical diagnosis. Its clinical manifestations may include menstrual irregularities, signs of androgen excess, and obesity. Insulin resistance and elevated serum LH levels are also common features in PCOS. PCOS is associated with an increased risk of type 2 diabetes and cardiovascular events, (**Revised 2003 consensus on diagnostic criteria and long-term health risks related toPCOS,ESHRE).**

PCOS appears to be associated with an increased risk of metabolic aberrations, including insulin resistance and hyperinsulinism, type 2 diabetes mellitus, dyslipidemia, cardiovascular disease, and endometrial carcinoma ***(Dunaif et al 1995, Ehraman 1997, Legro et al 1999).***

Metabolic syndrome (MBS) is a disorder which is composed of the clustering of several metabolic abnormalities including glucose abnormalities, dyslipidemia, obesity and hypertension, ***(Alberti et al 1998).***

This syndrome was first proposed by Reaven, (Reaven G 1988), and several studies have been reported in several names, the syndrome X,

the insulin resistance syndrome, and the dysmetabolic syndrome, for instance, ***(Alberti et al 1998 , Groop et al 2001).***

Studies revealed a higher prevalence of MBS in women with PCOS compared with age-matched women in the general U.S. population. the prevalence of the MBS in women with PCOS was 43%, which is nearly 2-fold higher than the age-adjusted prevalence rate of 24% in women nationally, based on data obtained from women who participated in the NHANES III survey, ***(Ford et al; 2002).***

Dislipidemia is one of the main components odf Metabolic syndrome The dyslipidemic components of the metabolic syndrome, is in the form of high TG and a low HDL-C concentration, are the ATP III criteria linked most closely to both insulin resistance and CVD risk. For example, differences in plasma TG concentration can account for ~36% of the variation in insulin-mediated glucose disposal in the same population in which fasting plasma glucose concentration accounted for only 5%–15% of the variability. Indeed, the relationship between plasma TG concentration and insulin-mediated glucose disposal is comparable to that between fasting plasma insulin concentration and insulin action, a commonly used surrogate estimate of insulin resistance ***(Yeni-Komshian et al; 2000).***

The combination of raised triglyceride and decreased high density lipoprotein is strongly linked with cardiovascular disease, ***(Wild R 1997).***

Hence, an increased risk of cardiovascular disease due to lipid perturbances will present in early adult life. Women with polycystic ovarian syndrome also show elevated concentrations of plasminogen activator inhibitor 1, ***(Ehramann et al 1997)*** , a potent inhibitor of

fibrinolysis, which have been shown to predict the occurrence of myocardial infarction. Suppression of hyperandrogenaemia by use of gonadotrophin releasing hormone analogues has little effect on the insulin resistance or the dyslipidaemia, suggesting that the abnormal lipid profile is independent of the raised androgen concentrations ***(Dunaif A 1995).***

Studies of women undergoing coronary angiography for evaluation of chest pain found a disproportionately large number with polycystic ovaries on ultrasound scan, ***(Birdsall et al; 1997).***

Furthermore, on multiple linear regression analysis the presence of polycystic ovaries was independently associated with the severity of the coronary vascular disease. Models using triglyceride concentrations, waist to hip ratio, non-insulin dependent diabetes, and elevated blood pressure in women with polycystic ovarian syndrome indicate a 7.4-fold increased risk of myocardial infarction compared with age matched referents, (***Dahlgren et al; 1992).***

From that we can say that the consequences of the polycystic ovary syndrome extend beyond the reproductive axis; women with the disorder are at substantial risk for the development of metabolic and cardiovascular abnormalities similar to those that make up the metabolic syndrome, (***Glueck et al; 2003).***

According to these findings it was the aim of the current study which was two objectives. First objective was to find out the prevalence of metabolic syndrome among patients with PCOS both obese and non-obese. The second objective was to detect the relation between insulin resistance and metabolic syndrome among PCOS patients both obese and non-obese.

In this cross sectional study 160 selected women were divided into *two groups:* ***I.*** **Study group:** including 80 young women with polycystic ovary syndrome (PCOS) [age 26 ± 4.5 years, 40 were obese with body mass index (BMI) 36 ± 3.92 kg/m^2; mean ± SD], 40 were non obese with body mass index (BMI) 24 ± 1.94 kg/m^2; mean ± SD].

II. Control group: included 80 age-matched females [age 26.5 ± 4.29, 40 were obese with body mass index (BMI) 35 ± 3.78 kg/m^2; mean ± SD], 40 were non obese with body mass index (BMI) 24 ± 2.36 kg/m^2; mean ± SD]. All were evaluated for the prevelance of insulin resistance and the occurrence of features of metabolic syndrome according to the Adult Treatment Panel III.

Regarding Hormonal parameters which were used as part of diagnosis for the presence of PCO. Serum LH & Free Testosterone were significantly high (P = 0.002 & 0.007 respectively), amoung non-obese PCOS patients both compared to non-obese control subjects, Level of serum FSH shows no significal difference (P > 0.05), ***(Results are presented in Table 6, & Figure 11).***

In our study as regard the prevelance of Metabolic syndrome among obese PCOS patients it was 45 % compared to 15 % amoung obese control group. And was 40 % amoung non-obese PCOS compared to 5 % amoung non-obese control group, . These results were with significant statistical difference (*P* = 0.001), ***(Results are shown in table "10" & fig "15".***

This is similar to that found by Ford 2002 which revealed a higher prevalence of MBS in women with PCOS compared with age-matched women in the general U.S. population. the prevalence of the MBS in women with PCOS was 43%, which is nearly 2-fold higher than the age-

adjusted prevalence rate of 24% in women nationally, based on data obtained from women who participated in the NHANES III survey, ***(Ford et al; 2002).***

Also, MBS was diagnosed in 34.9% of women with PCOS versus 6.8% of the controls ($P < 0.001$). When adjusted for age, the prevalence was 47.3% and 4.3% in the PCOS and control group, respectively. In all age groups the prevalence of MS was greatest in women with PCOS, those aged <30 years being at particular risk ($P < 0.001$), (***Ricardo Azziz 2006***).

Vural *et al*. evaluated 43 women with PCOS and 43 age-matched controls. Using the WHO criteria, 11.6% of women with PCOS were diagnosed as having MS; alternatively, if the NCEP ATP III criteria were used, only 2.3% of PCOS patients were affected with MBS, ***(Vural B et al. 2005).***

On the other hand,a lower prevalence was observed in Europe, being 1.6 % in the Czech Republic ***(Vrbikova et al 2005)***, 2.3 % in Turkey ***(Vural et al 2005)***, and 8.2 % to 16 % in Southern Italy ***(Carmina et al 2006).***

This finding is not surprising, since both the polycystic ovary syndrome and the metabolic syndrome share insulin resistance as a central pathogenetic feature. The polycystic ovary syndrome might thus be viewed as a sex-specific form of the metabolic syndrome, ***(National Cholesterol Education Program; 2002)***, and the term "syndrome XX" has been suggested as an apt term to underscore this association, **(Sam et al; 2003)**.

By comparing the prevalence of metabolic syndrom, low HDL levels, High triglycerides, High Blood pressure, and prevalence of insulin

resistance. among PCOS patients both obese and non obese we found no significant difference. This suggests that obesity alone does not explain the dyslipidemia and high prevalence of MBS found among PCOS patients***.(Results are shown in table "13").***

This is similar to results reported by Robert Wild Results of the study suggest that excess weight alone does not readily explain the dyslipidelmia observed in PCOS patients, ***(Wild et al., 1988)***. Also, Rosenhaum reported that that decreased insulin responsiveness in PCOS adipocytes is secondary to decreased levels of Glucose transporter proteins (GLUTp), this defect is also independent of obesity, glucose intolerance and sex hormone. Because the GLUTp is not expressed in fibroblasts, it is not possible to tell whether changes in GLUTp abundance in PCOS are an intrinsic defect or secondary to the already identified abnormalities in insulin receptor signal transduction ***(Rosenhaum et al., 1993).***

In further evaluation in the current study Individuals of metaolic syndrome were also evaluated among all subjects included in this study, obese women with PCOS had one abnormality of MBS presents 90% compared to 77.5% among obese control group. 77.5 % of obese PCOS patients had two or more abnormality, compared to 45 % among obese control group.

As regard non-obese women with PCOS they had 77.5 % had one abnormality of MBS , compared to 20 % among non-obese control group. Also 55 % of non-obese PCOS patients had two or more

abnormality, compared to 10 % among obese control group. ***(These results are shown at table 12).***

This is similar to that found by ***Teimuraz*** who evaluated individual abnormalities of Mets among women with PCOS, it was noteworthy that the majority of women with PCOS had at least one abnormality of the MBS present (91%). Other than elevated BMI, 69% of women with PCOS had two or more of the abnormalities present. Conversely, only 9% of these women lacked any metabolic abnormalities,***(Teimuraz et al 2004).*** This is with results at US → The prevalence of two or more MBS components is 43.9%, showing that a large group is at risk for its development. Based on the data from the 2000 US census, an estimated 47 million US residents have the MetS ***(Ford et al; 2002).***

We also evaluated the prevalence of each metabolic individual among the four groups included in the study.

<u>As regard Adominal obesity</u> comparison between both groups both obese and non-obese results was statistically significant, Resultes revealed incidence of low HDL amoung obese PCOS women was 72.5 % compared to 50% amoung normal obese women, and was 25 % amoung non-obese PCOS compared to 5 % amoung normal non-obese women. ***(Results are shown in table "11" & fig "16".***

Increased adiposity, particularly visceral adiposity that is reflected by an elevated waist circumference (>88 cm [35 in.]) or waist-to-hip ratio, has been associated with hyperandrogenemia, insulin sensitivity, glucose intolerance, and dyslipidemia, Attenuation of insulin sensitivity, whether accomplished by weight loss or with medication, ameliorates (but not necessarily normalizes) many of the metabolic aberrations in women with

the polycystic ovary syndrome. ***(National Cholesterol Education Program; 2002)*** .

The principal features of the polycystic ovarian syndrome is that visceral distribution of body fat, common in the syndrome, is of greater consequence to the metabolic effects of insulin resistance than obesity per se ***(Despress et al; 1990).***

Central obesity and insulin resistance lead to an altered lipolytic response to insulin, with impaired suppression of release of free fatty acids from adipose tissue. An increased flux of free fatty acids from central sites enters the portal circulation, increasing the availability of substrate to the liver for triglyceride production. Furthermore, women with the syndrome exhibit increased activity of hepatic lipase, an enzyme responsible for the conversion of large lipoprotein particles to smaller, more atherogenic species. This explains the findings of reduced concentrations of high density lipoprotein cholesterol and increased levels of atherogenic, small, low density lipoprotein ***(Pirwan et al; 1997).***

As regard level of serum HDL comparison between both groups both obese and non-obese results were statistically significant (P = 0.01, Resultes revealed incidence of low HDL amoung obese PCOS women was 60 % compared to 30% amoung normal obese women, and was 62.5 % amoung non-obese PCOS compared to 12.5 % amoung normal non-obese women. This was due to hyperandrogenemia which has an adverse effect on serum lipopeoteins through effects on HDL ***(Results are shown in table "11" & fig "17").***

Our results were similar to that found in other studies which showed low HDL-C occurred most frequently (68%),***(Teimuraz et al 2004),*** Also Other studies revealed a positive correlation between

triglyceride levels and levels of free and total testosterone and a negative correlation between HDL cholesterol levels and total and free testosterone ***(Senoz et al., 1994).***

This results were explained by the influence of hyperandrogenism on low-density lipoprotein (LDL) and high density lipoprotein (HDL). It was found that hyperandrogenemia may have an adverse effect on serum lipopeoteins through effects on HDL. Hispanic women may have a higher level of the atherogenic lipoprotein phenotype b, which may increase their risk for atherosclerosis ***(Legro et al., 1999).***

As regard level of serum Triglycerides comparison between both groups both obese and non-obese results was also statistically significant, Resultes revealed incidence of low HDL amoung obese PCOS women was 37.5 % compared to 20 % amoung normal obese women, and was 35 % amoung non-obese PCOS compared to 7.5 % amoung normal non-obese women. ***(Results are shown in table "11" & fig "18").***

Other authors ***(Senoz et al., 1994)*** positively correlates between triglyceride levels and androgen levels. In an interesting study of Norman et al., a group of 118 women showing PCOS on vaginal ultrasound scan was divided into those who had no hyperandrogenemia (n=21) and those with increased androgen and a clinical presentation normally associated with PCOS (n=97). These were compared with a reference group of 26 normal subjects. Glucose intolerance, lipid concentrations and endocrine profile were compared between groups. It was stated that subjects with PCOS ovaries without hyperandrogenemia exhibit similar disturbances in insulin and lipid profiles as those with PCOS ***(Senoz et al., 1994).***

As regard Eleveted Blood pressure comparison between both groups both obese and non-obese results was statistically significant, Resultes revealed incidence of low HDL amoung obese PCOS women was 32.5 % compared to 20% amoung normal obese women, and was 32.5 % amoung non-obese PCOS compared to 10 % amoung normal non-obese women ***(Results are shown in table "11" & fig "20".***

Our results is similar to that found in other studies which revealed that Hypertension develops in some women with the PCOS during their reproductive years, (***Zimmermann et al; 1992 , Gluek et al; 2003),*** and sustained hypertension may develop in later life in women with the disorder, ***(Dahlgren & Johansson et al; 1992).***

This is explained by: Reduced vascular compliance, (***Kelly et al; 2002)***, and vascular endothelial dysfunction were noted in most, (***Kelly et al; 2002 , Paradisi et al; 2003 , Orio et al; 2004***), but not all ***(Mather et al; 2000),*** studies of women with the PCOS.

Furthermore, the degree of impairment in vascular reactivity is significantly greater than can be explained by obesity alone, ***(Kelly et al; 2002).***

Insulin-lowering therapies appear to improve the vascular endothelial dysfunction in patients with the PCOS, ***(Paradisi et al; 2003).***

A predisposition to macrovascular disease and thrombosis in women with the PCOS has also been described, ***(Yildiz et al; 2002 , Orio et al; 2004).***

A recent study of premenopausal women showed that those with the PCOS had a higher prevalence of coronary-artery calcification as

detected by electron-beam computed tomography, ***(Christian et al; 2003).***

Incr**ease**d levels of plasminogen-activator inhibitor type 1 may contribute to this risk, ***(Ehramann et al; 1997 , Atiomo et al; 1998).***

As regard Eleveted Blood sugar both fasting and post prandial, comparison between both groups both obese and non-obese results was statistically significant, Resultes revealed incidence of low HDL amoung obese PCOS women was 22.5 % compared to 15% amoung normal obese women, and was 32.5 % amoung non-obese PCOS compared to 7.5 % amoung normal non-obese women. ***(Results are shown in table ""11 & fig "19".***

Of the abnormalities present in affected women with PCOS, low HDL-C occurred most frequently (68%), followed in descending order by elevated BMI (67%), high blood pressure (45%), hypertriglyceridemia (35%), and high fasting serum glucose (4%). These findings are consistent with those of Legro *et al.* (26) who also reported a high prevalence (91%) of low serum HDL-C (<35 mg/dl) and a low prevalence of IFG (3%) in women with PCOS. Low serum HDL-C levels are known to predict an increased risk of cardiovascular disease independently of serum LDL-C, and recent studies have suggested that serum HDL-C may provide cardiovascular protection by direct endothelial effects via nitric oxide synthase. Another contributing factor to cardiovascular disease is hyperandrogenemia. Our results found serum free testosterone levels to be significantly higher in women with PCOS and the MBS compared with women with PCOS without the MBS ($P = 0.002$). Likewise, SHBG levels were significantly lower in PCOS in the presence of the MBS compared

with PCOS lacking the MBS (P = 0.001). Studies have shown that SHBG may be a surrogate marker of insulin resistance such that the lower the level of SHBG, the greater the degree of insulin resistance. Therefore, the significantly lower serum concentration of SHBG observed in PCOS women with the MBS compared with those without the MBS suggests a central role of insulin resistance in the MBS, ,***(Teimuraz et al 2004).***.

Insulin Resistance is defined as reduced hyperglycemic response to a given amount of insulin. Only recently was it realized that mild hyperinsulinemia and insulin resistance are common findings in PCOS ***(Burghen et al., 1980; Pasquali et al., 1983)*** and that a derangement of insulin secretion may represent a main component of the pathogenesis and the clinical expression of the syndrome ***(Dunaif et al., 1995).***

The presence of Insulin Resistance amoung patients with PCOS ***Dunaif et al (1987)***, described a significant impairment of glucose metabolism in obese patients with PCOS when compared with ovulatory women matched by age and weight. ***(Legro et al., 1999),***.

In our study As regard insulin resistance, there was a statistical difference between the study group and the control group. Insulin resistance was found out in 52.5% of the obese women with PCOS, compared to 7.5 % in normal obese cases, and was 55 % amoung non-obeses women with PCOS compared to 4 % in normal non-obese women, difference was statistically highly significant (P= 0.001), ***(Results are shown in table "9 & 13" & fig "21 & Fig 22".***

Obese women with PCOS also have a dyslipidemia. At least one abnormal lipid level is seen in 70% of women with PCOS, ***(Legro et al 2001).***

The pattern of dyslipidemia found in the metablic syndrome, which features elevated triglycerides and low HDL cholesterol, has been reported in association with obesity in PCOS, but this has not been found to differ from weight-matched control subjects, ***(Holte et al 1994).***

As regard obesity as the cause of dyslipidemia in PCOS, ***(Jacobs et al.1987; Rojanasakul et al., 1988)***. 54 PCOS patients were divided into three groups according to body mass index (non obese '27', overweight '13' and obese '14'), all groups had a similar age and height, All PCOS patients with different BMI had similar hormonal profiles of PCOS which were different from the control. The dyslipidemia in form of elevated levels of cholesterol, triglyceride, LDL and decreased HDL was markedly observed only in the obese group, ***(Rojanasakul et al. 1988)***.

Studies showed that women with PCOS have disturbed lipoprotein lipid profile. Android type obesity is present in 40-50% of the patients **(*Kiddy et al.,1990; Dror Meirow et al., 1996)*** and is closely related to these disturbances, **(*Lapidus et al., 1984; Wild et al., 1988)***.

Hence, an increased risk of cardiovascular disease due to lipid disturbances will present in early adult life. Women with polycystic ovarian syndrome also show elevated concentrations of plasminogen activator inhibitor 1, ***(Ehramann et al 1997)*** ,

Insulin resistance occurs not only in obese women with PCOS where it might be expected because obesity is often associated with

insulin resistance but also in 50% of normal weight women with PCOS ***(Chang et al., 1983; Buyalas et al., 1996).*** In those patients, fasting serum insulin levels are higher when compared to controls of the same body weight. The overall prevalence of documented insulin resistance is approximately 70%-75% in PCOS women patients ***(Conway et al., 1990).***

PCOS patients have dyslipidemia and disturbed lipid profile, when divided into insulin resistance and non insulin resistance. It was found that in insulin resistance group, insulin and DHEA-S were positively correlated with total cholesterol, LDL and TG and negatively with HDL. ***(Dror Mcirow et al., 1996).***

The most complicated relationship between insulin resistance/hyperinsulinemia, the ATP III version of the metabolic syndrome, and CVD relates to the role of essential hypertension. The problem stems from the fact that no more than 50% of patients with essential hypertension are insulin resistant ***(Zavaroni et al; 1992),*** but that it is this subset of patients who are at greatest CVD risk ***(Sheuh et al; 1992, Jeppesen et al; 2000, Jeppesen et al; 2001).***

The metabolic syndrome confers increased risk of cardiovascular disease, and the increased insulin resistance of women with PCOS and metabolic syndrome should confer increased risk of glucose intolerance. Since PCOS affects up to 10% of reproductive-age women, if the prevalence of the metabolic syndrome in PCOS women, both obese and non-obese, is approximately 40%, then nearly two women may be affected with concurrent PCOS and the metabolic syndrome.

These findings support the idea that PCOS should be considered a general health disorder with serious public health complications and

indicates that physicians should comprehensively screen all women with PCOS for early detection of metabolic syndrome in order to avoid the metabolic disorders associated with metabolic syndrome.

CVD risk was not increased in those patients who did not have the dyslipidemia characteristic of insulin resistance/hyperinsulinemia, ***(Jeppesen et al; 2001).***

Important retrospective studies provide evidence of increased risk of cardiovascular disorders. A study of women thought to have polycystic ovarian syndrome who were treated with ovarian wedge resection 20-30 years earlier showed that they were four times more likely to be receiving treatment for hypertension than age and weight matched controls and seven times more likely to have a diagnosis of diabetes, ***(Dahlgreen et al; 1992).***

The evidence summarized above provides substantial support for the view that the CVD risk associated with increases in blood pressure is significantly increased when the hemodynamic abnormality is present in insulin-resistant individuals.