MEMBRANE FATTY ACIDS IN NORMAL AND EXPERIMENTALLY INDUCED DIABETES MELLITUS IN RATS

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ABSTRACT

Membrane fatty acids in normal and experimentally induced diabetes mellitus in rats were investigated. This study was carried out on 120 male rats. The rats were divided into two equal groups of 60 rats each. **Group I:** (Control group): Injected with citrate buffer only. **Group II:** (Diabetic group): Injected with a single intraperitoneal (i.p) injection of 50 mg/kg of streptozotocin for diabetes induction. Blood samples were collected in tubes containing trisodium citrate 3.8% from all animal groups five times at 2, 4, 6, 8 and 10 weeks from the onset of diabetes induction. Plasma were separated and processed directly for glucose, total cholesterol, triacylglycerols, HDL-C, LDL-C, VLDL-C, NEFA, and L-malondialdehyde (L-MDA) determination. Moreover, total cholesterol, phospholipids and fatty acids composition in erythrocyte membrane were also analyzed. The obtained results revealed that, a significant increase in plasma glucose, total cholesterol, triacylglycerols, LDL-C, VLDL-C, NEFA, L-MDA and significant decrease in HDL-C concentrations were observed in streptozotocin-induced diabetic rats when compared with the non-diabetic control group. Also, a marked decrease in total cholesterol and Phospholipids concentrations were observed in erythrocyte membrane in streptozotocin-induced diabetic (STZ-D) rats. Moreover, fatty acid composition in erythrocytes of STZ-D rats revealed significant decrease in the percent of pentadecyclic and palmitic acids and increase in stearic and arachidic acids percent during different periods of diabetes. From the obtained results it could be concluded that, experimental diabetes mellitus extensively alters and induced disturbances in lipid metabolism in male rats. Also, Streptozotocin induced diabetes in rats alters erythrocyte membrane fatty acid composition.

INTRODUCTION

Diabetes mellitus is found in almost all populations and is emerging as a growing problem in developing countries [Mahesh and Menon (2004)]. Diabetic patients appear to have an increased incidence of multiple cardiovascular diseases including atherosclerosis, myocardial infarction and congestive heart failure. Furthermore, diabetes often involves a cardiomyopathy which is usually associated with decreased glucose utilization and increased fatty acid oxidation at specific metabolic sites [Durbyak et al., 1994].

Fatty acid composition is changed in humans and animals with diabetes. Diabetes inhibits delta-6-desaturase, which converts linoleic acid (LA) into gamma linolenic acid (GLA), the precursor of arachidonic acid and ultimately several vasoactive prostanoids. In experimental and clinical diabetes, GLA production is reduced. Consequently, the levels of dihomo gamma linolenic acid (DGLA), which is a product of GLA elongation, and
arachidonic acid. Also are reduced, which results in a decreased production of the prostanoids, prostacyclin, and prostaglandins (Tsimaratos et al., 2001).

Free fatty acids are an improved physiological fuel for islets, and act as a supplemental nutrient secretagogue to potentiate insulin release acutely in the presence of glucose (Stein et al., 1997). Chronically elevated FFA are believed to play a role in the pathogenesis of certain forms of type H diabetes by both inhibiting insulin stimulated peripheral glucose uptake and contributing to B cell dysfunction (Boden, 1997).

Accordingly, this study was performed to investigate whether streptozotocin-induced diabetes in rats results in alters cholesterol, phospholipids and fatty acids composition of erythrocytes membrane. Moreover, alterations of some plasma lipids composition and lipoprotein profiles as well as lipid peroxidation in diabetic rats were also investigated. The determination of cholesterol, phospholipids and fatty acids composition of erythrocytes membrane in STZ-D rats are useful in establishing the protective role of essential fatty acid nutrient on catabolic consequence of diabetes mellitus induced biochemical abnormalities in male rats.

**MATERIALS AND METHODS**

One hundred and twenty white male albino rats, 12-16 weeks old and average body weight 220-250 gm were used in this study. Rats were obtained from laboratory animals research center, Faculty of Veterinary Medicine, Moshtohor, Benha University. Rats were housed in separated metal cages and kept at constant environmental and nutritional conditions throughout the period of experiment. Water was supplied ad-libitum.

**Experimental design:**

The rats were randomly divided into two main large equal groups, of 60 animals each, placed in individual cages and classified as follows:

**Group I: (Control group):** Injected with citrate buffer only. **Group II: (Diabetic group):** Injected with streptozotocin after overnight fasting for diabetes induction.

**Diabetes Induction:**

Rats were fasted for 18 hour and allowed free access of water. The experimental induction of diabetes in male rats was induced by a single intraperetinoel (i.p) injection of 50 mg / kg of streptozotocin (STZ) (sigma Chemical Co. P.O. Box. 14508, St. Lowis, U.S.A.) freshly dissolved in citrate buffer, PH 4.5. A week later, STZ-treated rats were fasted for 12 hour, and blood samples were collected from the orbital venous sinus for glucose
determination. Only those rats in diabetic group (group II) with blood glucose levels higher than 250 mg/dl were considered diabetic (Ramanathan et al., 1999).

**Sampling:**

Blood samples were collected after overnight fasting by ocular vein puncture from all animal groups, five times, at 2, 4, 6, 8 and 10 weeks from the onset of diabetes induction. Blood samples were collected in screw capped tubes containing an anticoagulant solution, trisodium citrate 3.8% with PH adjusted to 7.4 with citric acid (1 vol. anticoagulant / 9 vol. blood) and plasma were separated by centrifugation at 2500 r.p.m for 15 minutes. The clean, clear plasma was separated and processed directly for glucose determination, then kept in a deep freeze at – 20°C until used for subsequent biochemical analysis.

**Biochemical analysis:**

Plasma glucose, total cholesterol, triacylglycerols, high density lipoprotein cholesterol (HDL-cholesterol), Low density lipoprotein cholesterol (LDL-cholesterol), very low density lipoprotein cholesterol (VLDL-cholesterol), nonesterified fatty acids (NEFA), and L-malondialdehyde (L-MDA) were analyzed colorimetrically according to the methods described by Trinder (1969), Allain et al., (1974), Bucolo and David (1973), Grove (1979), Friedewald, (1972), Bauer, (1982), Schuster, (1979), and Esterbauer et al., (1982), respectively. Moreover, after plasma separation, erythrocytes were washed for plasma membrane isolation as described by Peuchant et al., (1989) and processed for determination of total cholesterol and phospholipids according to the methods described by Allain et al., (1974) and Takeyama, (1977), respectively. The methyl ester of fatty acids composition in erythrocyte membrane, were dissolved in pure chloroform and an aliquots of this solution were subjected to gas-liquid chromatography (GLC) analysis, according to the method of Vogel, (1975).

**Statistical analysis:**

Statistical analysis of the results was carried out using student’s T-test according to Kempthorn (1969).

**RESULTS AND DISCUSSION**

Diabetes represents a common endocrinal disease affecting many metabolic aspects joined mainly with absolute or relative deficiencies in insulin secretion and / or insulin sensitivity (Peters and Schringer, 1998). Such disease can be characterized by its long-term complications clearly observed in cardiovascular, renal, neural, and visual systems (Clin et al., 1997). Development of these complications appears to be somewhat related to duration of
the disease, specifically prolonged exposure to extreme high glucose level or its metabolites (Wang and Korc, 1995).

The obtained results (Table 1) revealed a significant increase in plasma glucose, total cholesterol, triacylglycerols, LDL-C, VLDL-C, NEFA, L-MDA and significant decrease in HDL-C concentrations in streptozotocin-induced diabetic rats when compared with the non-diabetic control group.

The increase in plasma glucose concentration of streptozotocin treated group which came in agreement with Nielsen et al., (1999) who related the developed hyperglycemia to the specific toxic effects have been attributed to STZ uptake through glucose transporter-2 (GLUT-2), these toxic effects lead to end organ damage through activation of the aldose-reductase pathway leading to toxic accumulation of sorbitol in nervous system (Greene et al., 1987), increased diacylglycerols synthesis with consequent activation of protein kinase C isoform (PKC) in vascular tissue, initiating diabetic complications and Increased oxidative stress with subsequent alterations in cellular redox balance (Williamson et al., 1993).

Regarding, plasma total cholesterol concentration in streptozotocin-induced diabetic (STZ-D) rats the obtained results are nearly similar to the reported studies of (Yeh et al., 1998) who demonstrated that, dyslipidemia is prominent in diabetic and renal failure patients showed TC, TG and LDL-C increase, additionally this atherogenic indexes in agreement with reported studies of (Goldfard-Rumyantzev and Passas, 2002), who related the atherosclerosis complications and higher in TG level is predominantly due to reduced lipolysis of triglyceride-rich lipoproteins. In diabetes glycoxidation could be an important pathway for accelerated LDL oxidation through the formation of the reactive oxygen species. So, glycoxidation induced significant damage to lipoproteins (Brownlee, 1996). In this respect, the characteristic lipid abnormalities in diabetes include higher level of TG, LDL-C, VLDL-C and decreased level of HDL-C. It’s the deficiency of insulin may decrease the rates of triacylglycerols removal either from the liver or the circulation (Yoshino et al., 1992) which could be also related to the increased activities of HMG-CoA as recorded by (Jiao et al., 1991) who observed that, plasma cholesterol was significantly increased and both hepatic and intestinal 3-hydroxy-3-methylglutaryl (HMG)-CoA reductase activities were significantly higher in Wister fatty rats than those in controls, respectively. On the other hand, ACAT activities in Wister fatty rats were significantly increased in the intestine and decreased in the liver in comparison with controls.
The increase in plasma triacylglycerols concentration were came in accordance with the recorded data of (Stein et al., 1995) who reported that, hypertriglyceridemia and hypercholesterolemia are frequently observed in diabetics. Increased lipolysis in diabetes may lead to an increased serum level of free fatty acids and glycerol, ketone bodies formation and lastly acidosis. Also, Ahmed et al., (2001) showed that, there was a significant increase in plasma non-esterified cholesterol, triglycerides and phospholipids in STZ-induced diabetic rats, accompanied by a decrease in high density lipoprotein (HDL)-cholesterol. The reported changes in TG could be related to the mild but significant insulin deficiency resulted in mild hypertriglyceridemia, linked to impaired triglyceride removal rather than to an overproduction of VLDL-triglyceride, despite elevated levels of plasma free fatty acids, also it could be attributed to the disturbed tissue lipases system which regulated by insulin were suppressed by STZ increasing TG (Gorska, et al., 1990).

In the present study diabetes is associated with lower level of HDL-C and increase level of LDL-C, and VLDL-C. Similarly, Assumpta et al., (1997) showed that, low density lipoprotein (LDL), and very low density lipoprotein (VLDL) demonstrate higher level. The recorded data may be due to deficiency of lipoprotein lipase activity (LPL : insulin dependent enzyme) which plays certain roles in both triacylglycerols removal and HDL-C production, such activity is usually attributed to insulin deficiency (De-Fronzo and Ferrannins, 1991). Moreover the hypertriglyceridemia observed here may be due to either a defect in lipoprotein removal from the plasma or to over production of LDL by the liver defect of removal of these panicles may be due to decreased lipoprotein lipase activity an insulin dependent enzyme (Tsutsumi et al., 1993). Triglycerides - rich lipoprotein are occurring simultaneously with decreased HDL-C level that lipoprotein abnormalities are commonly observed in diabetics and expressed as risk factors to atherosclerosis development. Hennig and Dupont (1983) recorded that, diabetes resulted in a decrease in HDL-cholesterol. Diabetes resulted in an increase in LDL-apoB but a decrease in LDL-apoE. Who suggested that, hyperlipidemia and low HDL cholesterol levels may be risk factors for the onset of diabetic cataracts and that diabetic cataracts may be accelerated by hyperlipidemia and low HDL cholesterol in rats. Moreover, Tsutsumi et al., (1999) recorded that, concentrations of very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL) of spontaneously diabetic BB and non diabetic littermate rats were higher than those of normal rats.
The recorded decrease in plasma NEFA concentration in diabetic rats was in accordance with the results of (Sivan, et al., 1998) who recorded that, increased lipolysis in diabetes may lead to an increased serum level of free fatty acids and glycerol, ketone bodies formation and lastly acidosis. Increased levels of plasma TGs and NEFA may play certain role in the pathogenesis of insulin-resistant diabetes. In the liver increased NEFA oxidation may stimulate gluconeogenesis, contributing in turn to in appropriate glucose production found in type II diabetic patients. The recorded data could be related to the escaping immediate uptake is a highly regulated process and that impairment of this extraction or entrapment of TG-derived FA may be involved in the pathophysiology of insulin resistance and dyslipidemia as conformed by Giron et al., (1999) who reported that, an increase in plasma and liver microsome oleic acid and a decrease in arachidonic acid were found in diabetes and Mello et al., (1988) demonstrated that, fasted streptozotocin-induced diabetic animals have increased NEFA levels also Iguchi et al., (1991) observed that, in contrast, the plasma levels of ketone bodies and FFA were significantly increased in STZ-diabetic rats.

The recorded data showed a significant increase in plasma L-MDA in the STZ diabetic rats. Similar results were recorded by Sunduram et al., (1996) who demonstrated that, plasma MDA showed 80 % increase in the early stages of diabetes, and more progressive increase later which explained as the factors favoring the formation of reactive oxygen species may catalyze lipid peroxidation in the plasma and other tissues and in poorly controlled diabetic, glucose oxidation through the pentose phosphate pathway initiates excessive formation of NADPH, this in turn can promote lipid peroxidation in the presence of cytochrome P- 450 system. The results could be related to the inactivation or inhibition of antioxidant enzymes through glycation, in poorly controlled diabetes mellitus, may give rise high lipid peroxidation rate, evidence of lipid peroxidation had been observed in many diabetic complications.

The obtained results (Table 2) revealed a marked decrease in total cholesterol and phospholipids concentrations of erythrocyte membrane in streptozotocin-induced diabetic rats. Similarly, Le Petit et al., (1988) reported that, the acylation of total phospholipids with palmetic, oleic, or arachidonic acids were decreased in intact erythrocytes from diabetic animals. It also could be attributed to that the erythrocyte membrane composition is altered both in hyperglycemic and hyperlipidemic conditions, and may provide a useful model for evaluating lipid carbohydrate abnormalities of membrane structures in diabetes mellitus Arduini , et al., (1990). Also, the membrane cholesterol/phospholipids ratio is the main
reason for decreased membrane fluidity in diabetes, also the composition and structural changes in erythrocyte membranes and compositional changes in plasma lipids may contribute to the development of diabetic complications in diabetes as reported by Bryszewska et al., (1986). In this respect Prakasham et al., (2003) showed that, a significant elevation of erythrocyte thiobarbituric acid reactive substances (TBARS), an index of lipid peroxidation and significant reduction in membrane cholesterol and phospholipids content were observed in STZ diabetic rats and the diabetic strain revealed a significant fall in the amount of linoleic acid in liver and kidney microsomes and in erythrocyte membranes.

The obtained results (Table 3) demonstrated that, Fatty acid composition in erythrocytes of (STZ-D) rats revealed significant decrease in the percent of pentadecyclic and palmitic acids and increase in stearic and arachidic acids during different periods of diabetes. Conversely, the total amount of saturated fatty acids was significantly increased and the polyunsaturated/saturated ratio was decreased in the Type 1 diabetic patients. On the other hand, in the erythrocyte membrane, linoleic and stearic acid were higher, and palmitic, palmitoleic, and arachidonic acid were lower in diabetic rats. The activities of delta 6 desaturase in diabetic rats were 68% of those of controls, and increased to 119% of controls after insulin treatment. These changes may be related to the changes in radioactive fatty acid incorporation were found in diabetic red cell phosphatidylethanolamine (PE), though they were not statistically significant. The analysis of the membrane phospholipids fatty acid composition revealed a consistent increase of linoleate levels in diabetic rat red cells, a modest decrease of palmitate, oleate and arachidonate. Lysophosphatidylcholine acyl-CoA transferase (LAT) specific activity measured with either palmitoyl-CoA or oleyl-CoA was significantly reduced in diabetic erythrocyte membranes in comparison to controls and due to the platelet-poor plasma (PPP), the most significant increases in free fatty acids were stearate, linoleate, eicosatrienoate (n-6), and docosahexaenoate (n-3). Also, fatty acid composition of RBC phospholipids was also altered, with significant decreases in arachidonate, docosatetraenoate (n-6), and docosapentaenoate (n-6) and increases in linoleate and docosahexaenoate as shown by Arduini et al., (1995).

From the obtained results it could be concluded that, experimental induced diabetes mellitus in rats extensively alters and induced disturbances in lipid metabolism. Moreover, composition and structural changes in erythrocyte membranes lipids as well as plasma lipids may contribute to the development of diabetic complications. Because, diabetes induced major changes in plasma and red cell membrane lipid compositions. Therefore, we
recommended that, equivalent and adequate amounts of dietary polyunsaturated fatty acids are very essential and should be used with save and therapeutic dose level which may attenuate the adverse and dangerous effects of diabetes or may improve the progression of the disease.

REFERENCES


**Table (1):** Plasma Glucose, Total Cholesterol, Triglyceric serum, HDL-C, LDL-C, VLDL-C (mg/dL), NEFA (mmol/L) and L - MDA (nmol/L) concentrations in streptozotocin-induced diabetic male rats and their control

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Diabetes</th>
<th>Two weeks</th>
<th>Four weeks</th>
<th>Six weeks</th>
<th>Eight weeks</th>
<th>Two weeks</th>
<th>Four weeks</th>
<th>Six weeks</th>
<th>Eight weeks</th>
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<tr>
<td>Glucose</td>
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<td>89.71</td>
<td>88.04</td>
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<td>87.31</td>
<td>87.08</td>
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<tr>
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<td>236.74</td>
<td>231.37</td>
<td>231.37</td>
<td>231.37</td>
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<td>231.37</td>
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<tr>
<td>HDL-C</td>
<td>41.39</td>
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<td>41.39</td>
<td>41.39</td>
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<tr>
<td>LDL-C</td>
<td>185.76</td>
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<tr>
<td>VLDL-C</td>
<td>6.69</td>
<td>6.69</td>
<td>6.69</td>
<td>6.69</td>
<td>6.69</td>
<td>6.69</td>
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<tr>
<td>NEFA (mmol/L)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<tr>
<td>L - MDA (nmol/L)</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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<td>0.01</td>
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</table>

Data are presented as Mean ± S.E. * = Standard error, ** = Significantly different from control at P<0.05, *** = Highly significantly different fromControl (P<0.001)

**Table (2):** Total cholesterol and phospholipids concentrations of erythrocyte membrane in streptozotocin-induced diabetic male rats and their control (mmol/L)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Diabetes</th>
<th>Two weeks</th>
<th>Four weeks</th>
<th>Six weeks</th>
<th>Eight weeks</th>
<th>Two weeks</th>
<th>Four weeks</th>
<th>Six weeks</th>
<th>Eight weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phospholipids</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
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</table>

Data are presented as Mean ± S.E. * = Standard error, ** = Significantly different from control at P<0.01
الحمض الدهني في الفئران الطبيعية والمحذوف فيها مرض البول السكري تجريبياً

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الملخص العربي

يعتبر مرض البول السكري من أكثر الأمراض انتشاراً وشائعاً لتبقي في كثير من الأمراض مثل تصلب الشرايين وأرتفاع ضغط الدم. أيضاً لما يحدث من خلال زيادة في دهون الدم ومما جرى تكرار في البحث هذا البحث بهدف

معرفة التغيرات الكيميائية الحيوية للأحماض الدهنية المكونة لغشاء كريات الدم الحمراء وكذلك دهون بلازما الدم للمصابين مرض البول السكري المحدث تجريبياً في فئران التجربة باستخدام مادة الاستروزوتين. وجدت النتائج

الدراسة على عدد 120 من الفئران البيضاء تتراوح أعمارها بين أثنا عشر إلى ستة عشر أسعة وأوزانها بين 220 - 250 جرام قسمت إلى مجموعتين واصلت كل مجموعة على 60 فاراً وتوزيع كالآتي: المجموعة الأولى (المجموعة الضابطة) . المجموعة الثانية (المجموعة المحددة مرض البول السكري) ثم حقنها بمادة

استروزوتين في الغشاء البرونجوني بنسبة 50 ميلليجرام لكل كيلو جرام من وزن الجسم. ثم جمع عينات الدم من كل الحيوانات بعد 2, 4, 6, 8, 10 أسابيع في أنابيب مضفية بآليات سترات الصوديوم، وتم فصل البلازما استخدمت

باشرة لإجراء القياسات النيوكيميائية الآتية: الجلوكون، الكولسترول الكلي، ثلاثي الجليسريدات والدهون عالية الكثافة والدهون منخفضة الكثافة والدهون منخفضة الكثافة جداً والإحماض الدهنية الحرة إلـ: مالون داً أنهيد. كما

تم قياس الكولسترول الكلي والفسفوليبيدات والأحماض الدهنية في غشاء كريات الدم الحمراء. وقد أظهرت النتائج بعد تحليلها إحصائياً على التالي: - وجود زيادة منى في ترکيز الجلوكون، الكولسترول الكلي، ثلاثي الجليسريدات
الدهون منخفضة الكثافة والدهون منخفضة الكثافة جداً والأحماض الدهنية الحرة و إل-سالون دا أندنيد مع نقص في
مستوى الدهون عالية الكثافة في بلازما الدم بالإضافة إلى وجود نقص معنى في تركيز الكوليسترول الكلي والدهون
الفسفورية، وأيضا وجود نقص معنى في تركيز كلا من الحمض الدهني بنتاديسبيكلك والبالمتيك زيادة في تركيز
حمض الأراشيدك والأستباريك في غشاء كريات الدم الحمراء في الفئران المحدث فيها الداء السكري عند مقارنتها
بالمجموعة الضابطة أثناء بعض فترات التجربة. من ناحية أخرى أسفرت النتائج عن وجود نقص معنى في تركيز
كلا من الحمض الدهني بنتاديسبيكلك والبالمتيك مع وجود زيادة في تركيز حمض الأراشيدك والأستباريك في غشاء
كريات الدم الحمراء في الفئران المحدث بها الداء السكري أثناء بعض فترات التجربة. نظرًا لأن مرض الداء السكري
يسبب تغيرات كبيرة في مكونات دهون الدم وأيضا الدهون المكونة لغشاء كريات الدم الحمراء والذي يؤدي إلى حدوث
الكثير من المضاعفات والأمراض الأخرى المصاحبة له لذلك نوصي بتناول وجبات مناسبة وأمانة من الأحماض
الدهنية الغير مشبعة لما لها من دور أساسي في الوقاية من الآثار الضارة والخطيرة الناجمة من حدوث هذا المرض.