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Hypoglycemic Effect of Hazelnut and its Effect on Some Sex Hormones in Alloxan Induced Diabetic in Female Rats

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Abstract: Hazelnut is the second richest source of monounsaturated fatty acids among nuts and is rich in vitamins E and B6, phytosterols, folate, L-arginine, polyphenols and fiber. The present study aimed to investigate the hypoglycemic effect of hazelnut and its effect on some sex hormones in diabetic female rats. Animals were randomly assigned to five groups of equal number and weight. Group I, kept as a normal control group; Group II, kept as a diabetic control group, Groups III, IV and V, kept as diabetic groups and feeding supplemented diet with 5, 10 and 15% hazelnuts, respectively. Supplemented diet with 10% and 15% of hazelnut significantly lower food intake compare to the positive control group. Body weight gain significantly increased in treated diabetic group compare with the positive control group. Feeding supplemented diet with hazelnut at the three different levels caused significantly lower in concentrations of blood glucose, total lipids, triglycerides, total cholesterol, AST, ALT, blood urea nitrogen, uric acid and creatinine and significantly lower in levels of insulin, thyroid stimulating, follicle-stimulating and luteinizing hormones compared to that of untreated diabetic rats. Histological study showed hypertrophy and hyperplasia in beta-cells of islets of langerhans associated with pyknosis of their nuclei in positive control rats. Slight hypertrophy in islets of langerhans and congestion of pancreatic blood vessel was showed in pancreas sections of treated rats with 5 and 10% of hazelnut, respectively. However, rats treated with 15% of hazelnut showed apparent normal histological structure. Ovary sections of positive control rats showed dilation and congestion of blood vessel as well as interstitial connective tissue proliferation. Interstitial cells hyperplasia and follicles were showed in ovary of treated rats with 5 and 10% of hazelnut, respectively. Primary oocytes were showed in ovary sections of treated rats with 15% of hazelnut. In conclusions, hazelnut can be readily incorporated into healthy diet to its healthy effect benefits in diabetes and its complication.

Key words: Hazelnut, diabetes mellitus, thyroid, follicle stimulating hormone, luteinizing hormone, liver functions, kidney functions

INTRODUCTION

Diabetes mellitus is a disorder that affects the body ability to make or use insulin. Insulin is a hormone produced in the pancreas that helps transport glucose (blood sugar) from the bloodstream into the cells so they can break it down and use it for fuel. People cannot live without insulin. Diabetes results in abnormal levels of glucose in the bloodstream. This can cause severe short-term and long-term consequences ranging from brain damage to amputations and heart disease [American Diabetes Association (ADA), 2007].

Replacement of carbohydrate by healthy fat, such as mono and polyunsaturated fatty acids, has been increasingly recognized as a therapeutic strategy in the treatment of diabetes (Franz *et al*., 2002). At the same time increased proportions of fat and protein in the diet, especially of plant origin may confer metabolic benefits and reduce the risk of developing coronary heart disease and diabetes (Jenkins *et al*., 2009). However, there is little guidance on the optimal foods with which to increase the fat and protein intakes and fear persists that increasing the proportion of fat in the diet will increase body weight (Franz *et al*., 2002).

Traditional plant treatments for diabetes are used throughout the world but the most of evidence for their beneficial effects is anecdotal. After introduction of insulin therapy the use of traditional treatment for diabetes greatly declined, although some traditional practices are continued for prophylactic purpose and adjuncts to conventional therapy (Marles and Farnsworth, 1996). Nevertheless, use of nuts to increase fat intake has not resulted in weight gain and habitual nut consumption lowers LDL cholesterol. Furthermore, nut intake has been associated with reduced CHD risk, a major cause of death in diabetes (Sabate *et al*., 2010).

Hazelnut has a number of cardioprotective compounds including vitamin E (alpha-tocopherol isomer),

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phytosterols, vitamin B6, folate, L-arginine, polyphenols and fiber. In addition, it is the second richest source of Monounsaturated Fatty Acids (MUFAs) among nuts. It contains approximately 82-83% MUFAs, mainly oleic acid (18:1) and less than 7.7-8% saturated fatty acids (SFA) (Alasalvar *et al*., 2006). One of the most important features of the hazelnut, it has the highest ratio of unsaturated/saturated fatty acids (Sabate, 2003). In addition to MUFA, some other components found in hazelnut have been reported to reduce plasma total and LDL cholesterol concentrations, including PUFA (Feldman, 2002), phytosterols (Weststrate and Meijer, 1998) and soluble dietary fiber (Brown *et al*., 1999). A high fiber diet can benefit heart and digestive health and help manage blood glucose level (Anderson *et al*., 2009), Moreover, hazelnut is an excellent source of vitamin E (Alasalvar *et al*., 2003) which has been shown to reduce the risk of CHD (Rimm and Stampfer, 1997). This cardioprotective effect appears due to vitamin E-induced inhibition of LDL oxidation (Steinberg and Lewis, 1997). Whole nuts including hazelnut may provide a variety of non-fat cardioprotective constituents including arginine (Cooke and Tsao, 1997), copper (Klevay, 1993) and magnesium (Elin and Hosseini, 1993).

Nowadays there is an increasing demand for natural products with antidiabetic activities, since many therapeutically important compounds are derived from them. Therefore, the main objective of the present study was to investigate the antidiabetic effect of hazelnut and its effect on some sex hormones in diabetic female rats. This was achieved by measuring the serum concentration of blood glucose, insulin, Thyroid Stimulating (TSH), Follicle-stimulating (FSH) and Luteinizing Hormones (LH), Total Lipids (TL), Triglycerides (TG), Total Cholesterol (TC), Aspartate Aminotransferase (AST) and Alanine Aminotransferase (ALT), Blood Urea Nitrogen (BUN), Uric Acid (UA) and Creatinin (Cr) as well as histopathological examination of pancreas and ovary in diabetic rats.

MATERIALS AND METHODS

Materials

Rats and basal diet: Thirty five of female Sprague-Dawley rats weighing 200±5 g were purchased from the Laboratory Animal Colony, Ministry of Health and Population, Helwan, Egypt. Basal diet constituents were obtained from El- Gomhorya Company for Chemical and Pharmaceutical, Cairo, Egypt.

Hazelnuts: Hazelnuts were obtained from local market, Cairo Egypt.

Chemicals: Alloxan was purchased from El-Gomhorya Company for Pharmaceutical and Chemicals, Cairo, Egypt. Kits for biochemical analysis of serum insulin, TSH, FSH and LH hormones, TL, TG, TC, AST, ALT, BUN, UA and Cr were purchased from the Gamma Trade Company for Pharmaceutical and Chemicals, Dokki, Egypt.

Methods

Preparation of basal diet: The basal diet (AIN-93M) was prepared according to Reeves *et al*. (1993). Diet was formulated to meet the recommended nutrients levels for rats.

Induction of diabetes: Diabetes was induced by a single subcutaneous injection of alloxan dissolved in sterile normal saline at a dose of 150 mg/kg of body weight according to the method described by Buko *et al*. (1996). Non-diabetic control rats were injected with an equivalent amount of slain solution. Diabetic rats were kept for the next 24 hours on 10% glucose solution to prevent hypoglycemia. Seventy-two hours after injection with alloxan, the diabetic rats were confirmed by measuring the 4-h fasting blood glucose level from the tail vein. Animals with a blood glucose level above 300 mg/dl were considered diabetic and included in the experiment.

Experimental design: All animals were housed in plastic cages at 25±1°C, with a relative humidity of 40-60%, an alternating 12-hour light-dark cycle and were given free access to basal diets and water ad libitum. The animals were allowed to acclimatize to the laboratory environment for 7 days and then were randomly assigned to five groups of equal number and weight (seven animals each) as follows: Group I, normal control rats (negative control group) fed on the basal diet only; Group II, diabetic control rats (positive control group) fed on the basal diet only; Groups III, IV and V, diabetic rats fed on basal diet formulated with 5, 10 and 15% hazelnuts, respectively.

Food intake and body weight gain assay: Food Intake (FI) was calculated every other day. The biological value of the different diets was assessed by the determination of its effect on Body Weight Gain (BWG) at the end of the experimental period using the following formulas:

$$BWG = \text{Final Body Weight} - \text{Initial Body Weight}$$

At the end of the experimental period (6 weeks), diets were withheld from experimental rats for 12-h and then rats were sacrificed. Blood samples were collected from the portal vein into dry clean centrifuge tubes. For serum separation, blood samples were left at room temperature to get clot and then centrifuged for 15 minutes at 3000 rpm. Serum was carefully aspired using a needle and transfers into dry clean test tubes and kept frozen at -10°C until chemical analysis. Organs

such as pancreas and ovary were removed and washed with saline solution, dried and kept in formalin solution (10%) for histopathological examination.

Blood glucose level assay: Blood glucose concentrations were measured at the end of experimental period (6 weeks). Blood samples were collected by tail vein of the rats after the animals had been fasted for 12 hr and the blood glucose levels determinations were carried out by using a single touch Glucometer (Ascensia ENTRUST, Bayer) based on glucose oxidase.

Insulin level assay: Serum Insulin-like growth factor I (IGF-I) will be measured as described by (Posario, 2010).

Serum levels of TSH, FSH and LH hormones assay: Serum levels of TSH, FSH and LH hormones were measured quantitative by microplate immunoenzymateric assay as described by kits instructions (Monobind Inc. USA).

Serum levels of TL, TG and TC assay: Serum concentrations of TL were determined colorimetric using spectrophotometer apparatus adjust at 520nm as described by kit instructions (Randox Co. Ireland). Concentrations of serum TG and TC were determined using enzymatic methods as described in the instructions provided with the kits (Analyticon® Biotechnologies AG, Germany). The absorbance of the testes samples were read using spectrophotometer adjusted at 546 nm for TG and TC.

Liver functions assay: Serum AST and ALT activities were determined using colorimetric methods as described in the kits instruction (Diamond Co, Hannover, Germany). The absorption of test samples was read at 505nm for AST and ALT.

Kidney functions assay: Serum urea nitrogen and uric acid concentrations were determined by enzymatic colorimetric method and creatinin was determined using colorimetric kinetic as described by Young (2001).

Histopathological examination: Pancreas and ovary of the scarified rats were taken and immersed in 10% formalin solution. The fixed specimens were then trimmed, washed and dehydrated in ascending grades of alcohol. Specimens were then cleared in xylol, embedded in paraffin, sectioned at 4-6 microns thickness and stained with hematoxylin and eosin stain for examination of the pancreas and ovary as described by Carleton (1979).

Statistical analysis: All data were expressed as means±SE. Significant differences among the experimental groups were determined by one-way analysis of variance using the SPSS statistical analysis program. Statistical significance was considered at $p<0.05$.

RESULTS

Food intake and body weight gain: As shown in Table 1 recorded data revealed that diabetic control rats had no significant difference ($p<0.05$) in FI (13.29±0.29 g/d) and significant decreased in BWG (13.29±0.42g) compared to that of the normal control rats (13.57±0.20 g/d and 29±0.38 g, respectively). Feeding supplementing diet with 5% of hazelnut caused no significant decreased in FI (12.71±0.29 g/d) compare to the diabetic control group (13.29±0.29 g/d). However, supplemented diet with 10 and 15% of hazelnut caused significant decrease ($p<0.05$) in FI (12.14±0.26 g/d) compare to the diabetic control group. Body weight gain of treated diabetic group was increased significantly ($p<0.05$) as compare to the non treated diabetic control group.

Blood glucose levels and serum concentrations of insulin: Results in Table 2 shows significant increase in serum concentration of diabetic control rats (458.57±0.48 mg/dl) compared to the normal control rats (88.00±0.38 mg/dl). Diabetic treated rats with the three different levels of hazelnut have lower significantly in blood glucose levels (347.71±0.29, 257.71±0.29 and 123±0.22 mg/dl, respectively) compared to diabetic control rats (458.57±0.48 mg/dl).

Serum level of insulin was significantly ($P<0.05$) reduced in diabetic control group (6.31±0.004 µm/ml) compared

Table 1: Food intake and body weight gain in female rats

Groups		Parameters as Mean±SE FI (g/d)	BWG (g)
Normal control group (-ve)		13.57±0.20^{a}	29.00±0.38^{a}
Diabetic control group (+ve)		13.29±0.29^{ab}	13.29±0.42^{e}
Treated diabetic groups with hazelnut at levels of:	5%	12.71±0.29^{bc}	17.71±0.42^{d}
	10%	12.14±0.26^{c}	21.00±0.31^{c}
	15%	12.14±0.26^{c}	23.86±0.26^{b}

Means in each column with different superscript letters differ significantly at $p<0.05$.
A uses harmonic mean sample size = 7 rats.

Table 2: Blood glucose levels and serum concentrations of insulin in female rats

Groups		Parameters as Mean±SE BGL (mg/dl)	Insulin (µm/ml)
Normal control group (-ve)		88.00±0.38^{e}	13.56±0.14^{a}
Diabetic control group (+ve)		458.57±0.48^{a}	6.31±0.004^{c}
Treated diabetic groups with hazelnut at levels of:	5%	347.71±0.29^{b}	0.20±0.06^{d}
	10%	257.71±0.29^{c}	11.52±0.004^{c}
	15%	123.00±0.22^{d}	11.97±0.12^{b}

Means in each column with different superscript letters differ significantly at $p<0.05$.
A uses harmonic mean sample size = 7 rats.

Table 3: Serum concentrations of TSH, FSH and LH hormones in female rats

Groups		Parameters as Mean±SE TSH (mIU/ml)	FSH (mIU/ml)	LH (mIU/ml)
Normal control group (-ve)		1.71±0.03[a]	6.84±0.02[a]	19.31±0.23[a]
Diabetic control group (+ve)		0.36±0.02[d]	3.66±0.02[e]	2.87±0.21[e]
Treated diabetic groups with	5%	0.56±0.02[c]	4.27±0.05[d]	4.67±0.10[d]
hazelnut at levels of:	10%	0.81±0.03[b]	4.64±0.03[c]	9.33±0.33[c]
	15%	0.86±0.02[b]	5.69±0.03[b]	15.53±0.1[b]

Means in each column with different superscript letters differ significantly at p<0.05.
A uses harmonic mean sample size = 7 rats.

Table 4: Serum concentrations of TL, TG and TC in female rats

Groups		Parameters as Mean±SE TL (mg/dl)	TG (mg/dl)	TC (mg/dl)
Normal control group (-ve)		315.57±0.53[e]	43.57±0.30[e]	75.43±0.37[e]
Diabetic control group (+ve)		356.43±0.81[a]	64.71±0.18[a]	100.57±0.43[a]
Treated diabetic groups with	5%	353.29±0.29[b]	62.29±0.18[b]	97.57±0.30[b]
hazelnut at levels of:	10%	342.86±0.26[c]	54.71±0.42[c]	91.00±0.38[c]
	15%	333.86±0.34[d]	46.43±0.30[d]	86.57±0.48[d]

Means in each column with different superscript letters differ significantly at p<0.05.
A uses harmonic mean sample size = 7 rats.

to the normal control rats (13.56±0.14 µm/ml). Treated diabetic group with hazelnut at level of 5, 10 and 15% have significant increase (p<0.05) in serum insulin levels (10.20±0.06, 11.52±0.004 and 11.97±0.12 µm/ml, respectively) compared to the diabetic control rats (6.31±0.004 µm/ml). High level of hazelnut (15%) produced significant change in serum level of insulin compared to the other treated group.

Serum concentrations of TSH, FSH and LH hormones: Data of Serum levels of TSH, FSH and LH hormones are presented in Table 3. It revealed that diabetic control rats have significant (p<0.05) decrease in serum level of TSH, FSH and LH hormones compared to the normal control rats. Treated diabetic groups with hazelnut at the three different levels have significantly (p<0.05) higher in serum levels of TSH, FSH and LH hormones compared to the diabetic control group.

Serum concentrations of TL, TG and TC: As shows in Table 4, results indicated that there was significant (p<0.05) increase in serum concentrations of TL, TG and TC in diabetic control rats compared to the normal rats. Feeding supplemented diet with different levels of hazelnut caused (p<0.05) significant decrease in diabetic groups compared to diabetic control group.

Liver functions: Serum concentrations of AST and ALT are recorded in Table 5. The presented data showed that there is a significant increase (p<0.05) in serum level of AST and ALT (17.86±0.26 and 15.57±0.20 U/L, respectively) in diabetic control rats compared to the normal control rats (11.57±0.37 and 9.57±0.37U/L, respectively). Treated diabetic groups with the three different levels of hazelnuts resulted in significant

Table 5: Serum concentrations of AST and ALT in female rats

Groups		Parameters as Mean±SE AST (U/L)	ALT (U/L)
Normal control group (-ve)		11.57±0.37[d]	9.57±0.37[d]
Diabetic control group (+ve)		17.86±0.26[a]	15.57±0.20[a]
Treated diabetic groups with	5%	15.86±0.34[b]	13.57±0.37[b]
hazelnut at levels of:	10%	11.142±0.40[d]	9.29±0.36[d]
	15%	13.57±0.30[c]	11.29±0.29[c]

Means in each column with different superscript letters differ significantly at p<0.05.
A uses harmonic mean sample size = 7 rats.

(p<0.05) reduction in serum levels of AST and ALT compared to the diabetic control group. Treated diabetic rats with the higher levels of hazelnut have significantly lower in serum levels of AST and ALT compared to the other treated groups.

Kidney functions: Data in Table 6 shows significantly higher in serum concentrations of BUN, UA and Cr in diabetic control rats compared to the normal control groups. However, there was significant (p<0.05) decrease in treated diabetic rats with hazelnut compared to the diabetic control rats. High levels of hazelnut (15%) produced significantly lower in serum levels of BUN, UA and Cr compared to the other treated levels of hazelnut.

Histopathological examination: Pancreas sections of normal control group showed no histopathological change as shown in Fig. 1. In contrast, hypertrophy and hyperplasia of beta-cells of islets of langerhans associated with pyknosis of their nuclei were found in diabetic control rats as shown in Fig. 2. Slight hypertrophy of islets of langerhans was found in pancreas sections of treated rats with 5% hazelnut as shown in Fig. 3. Pancreas sections of treated rats with

Table 6: Serum concentrations of BUN, UA and CR in female rats

Groups		Parameters as Mean±SE BUN (mg/dL)	UA (mg/dL)	Cr (mg/dL)
Normal control group (-ve)		27.71±0.18[e]	31.00±0.31[e]	0.63±0.02[e]
Diabetic control group (+ve)		68.29±0.29[a]	78.29±0.42[a]	2.86±0.05[a]
Treated diabetic groups wit	5%	63.43±0.20[b]	72.14±0.74[b]	2.40±0.07[b]
hazelnut at levels of:	10%	57.43±0.30[c]	64.43±0.48[c]	1.87±0.03[c]
	15%	42.43±0.20[d]	53.15±0.74[d]	1.17±0.03[d]

Means in each column with different superscript letters differ significantly at p<0.05.
A uses harmonic mean sample size = 7 rats.

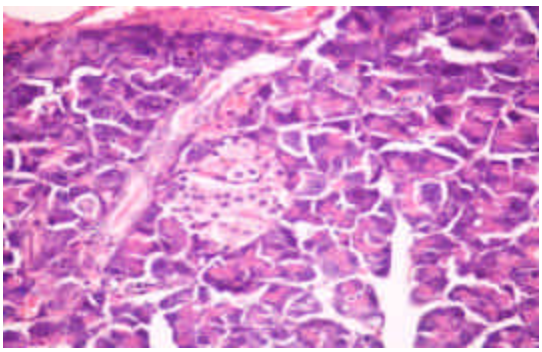

Fig. 1: Pancreas of normal control rats showing no histopathological changes (H and E x 400)

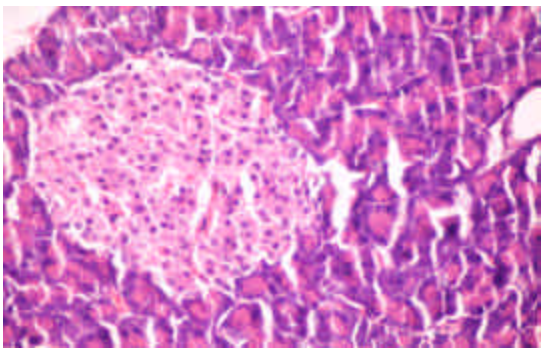

Fig. 3: Pancreas of treated rats with 5% of hazelnut showing slight hypertrophy of islets of langerhans (H and E x 400)

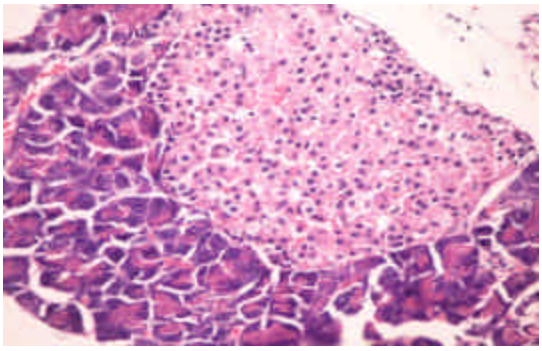

Fig. 2: Pancreas of diabetic control rats showing hypertrophy and hyperplasia of beta-cells of islets of langerhans associated with pyknosis of their nuclei (H and E x 400)

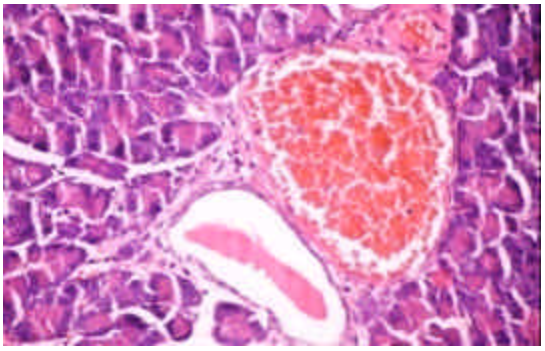

Fig. 4: Pancreas of treated rats with 10% of hazelnut showing congestion of pancreatic blood vessel (H and E x 400)

10% hazelnut revealed congestion of pancreatic blood vessel as shown in Fig. 4. However, rats treated with 15% of hazelnut showed no histopathological change.

Histopathological observation of ovary sections revealed no histological changes in normal control rats as shown in Fig. 5. Ovary sections of diabetic control rats showed dilation and congestion of blood vessel as well as interstitial connective tissue proliferation as shown in Fig. 6. Interstitial cells hyperplasia were showed in examined ovary of rats fed supplemented diet with 5% of hazelnut as shown in Fig. 7, whereas, ovary sections of treated rats with 10% of hazelnut showed follicles in ovary sections as shown in Fig. 8. Primary oocytes were showed in ovary sections of rats fed supplemented diet with 15% of hazelnut as shown in Fig. 9.

DISCUSSION

The hypoglycemic effect of hazelnut and its effect on sex hormone in diabetic female rats were investigated. Alloxan induced diabetes cause marked and significant increased in blood glucose level and serum concentrations of TL, TG, AST, ALT, BUN, UA and Cr,

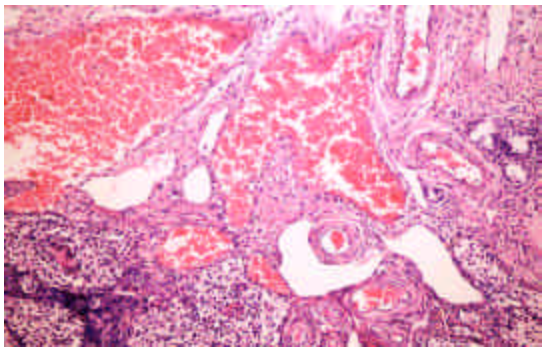

Fig. 5: Ovary of normal control group showing no histopathological changes (H and E X 400)

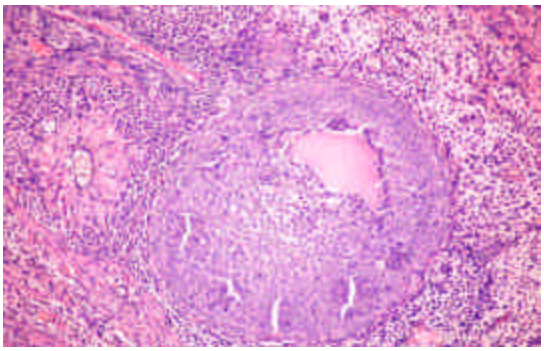

Fig. 6: Ovary of diabetic control group showing dilation and congestion of blood vessels as well as interstitial connective tissue proliferation (H and E x400)

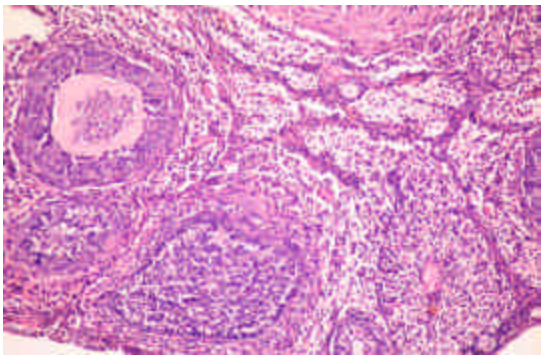

Fig. 7: Ovary of treated rats with 5% of hazelnut showing interstitial cells hyperplasia (H and E x 400)

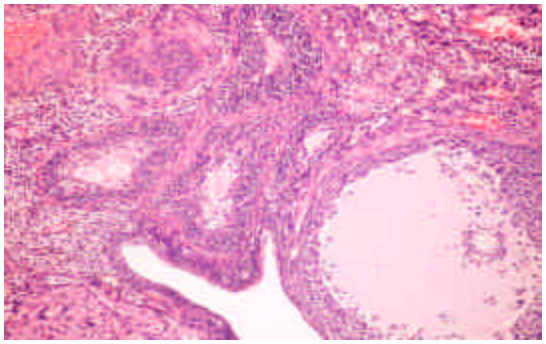

Fig. 8: Ovary of treated rats with 10% of hazelnut showing different stages of follicles (H and E x 200)

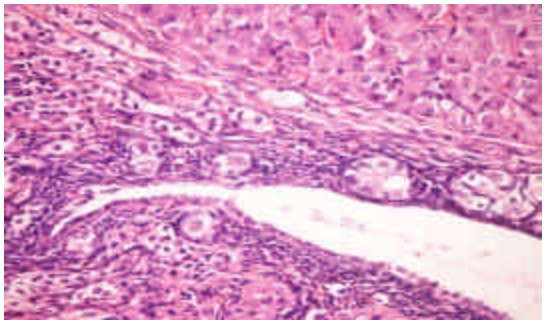

Fig. 9: Ovary of rats from treated group with 15% of hazelnut showing primary oocytes (H and E x 400)

significantly reduce BWG and serum concentrations of insulin, TSH, FSH, LH hormones compared to the normal control rats. These results were confirmed with histological changes in pancreas and ovary of diabetic rats. The present results was agreed with Lyra *et al.* (2006) who reported that chronic hyperglycemia of diabetes was associated with long term damage, dysfunction and failure of various organs. Laxmi *et al.* (2010) demonstrated that there was extensive damage of the langerhans in alloxan induces diabetic rats. High blood glucose level cause deterioration of pancreatic beta-cells due to oxidative stress.

Lack of insulin in diabetic rats can affect the serum FSH levels (Oksanen, 1975). The FSH acts synergistically with the LH in stimulation of androgen synthesis therefore, the reduction of this gonadotropin can play an important role in decrement of testosterone output in diabetic animals (Orth *et al.*, 1979). Diabetic patients suffer from deficiency in sexual function including libido and fertility (Jiang, 1996). Diabetes mellitus-induced hyperglycemia causes acute or chronic side effects that can affect all systems and organs such as sexual glands (Mallick *et al.*, 2007) caused reduction in the serum level of FSH and progesterone in female rats (Ballester *et al.*, 2007) and in blood plasma LH levels which is responsible for normal function of Leydig cells (Khaki *et al.*, 2009).

One of the probable mechanisms by which diabetes mellitus is involved in hyperglycemia and

hypercholesterolemia is oxidative stress exhibiting effects which leads to tissue destruction and dysfunction (Hemalatha *et al*., 2004). Diabetes is associated with increased dyslipidaemia (Daniel *et al*., 2003) characterized by elevated serum levels of TG and LDL-C (Florkowski, 2002) and TC (Farombi and Ige, 2007). The higher level of serum lipid is mainly due to the decrease in the action of lipolytic hormones in fat depots due to insulin action. Under normal circumstances, insulin activates the enzyme lipoprotein lipase which hydrolysis triglycerides. In diabetes, lipoprotein lipase is not activating due to insulin deficiency resulting in hypertriglyceridemia and hypercholestermia (Sharma *et al*., 2003). In diabetic rats, the utilization of impaired carbohydrate leads to accelerate lipolysis, resulted in hyperlipidaemia and increased lipid peroxidation which is associated with hyperlipidaemia (Granner, 1996).

Increased generation of free radicals due to oxidative stress may develop several adverse effects in diabetes mellitus such as hepathology and nephropathy disorders (Hamden *et al*., 2008). Therefore the elevation in serum AST, ALT and ALP may be results in response to oxidative process (Bansal *et al*., 2006). Oxidative stress is a common pathogenetic mechanism contributing to initiation and progression of hepatic damage in a variety of liver disorders (Medina and Moreno-Otero, 2005). Hyperglycemia increases the generation of free radicals by glucose auto-oxidation and the increment of free radicals may lead to liver cell damage and increased the activities of AST, ALT in the serum of diabetic animals (Ana Angelica *et al*., 2009).

Chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, especially kidneys, heart and blood vessels (Uladimir, 2003). Diabetic rats had a significant increase in creatinin and urea levels as compared to the normal animals. Kidney dysfunctions in the diabetic rats may be related to the generation of reactive oxygen species and lipid peroxidation which are associated with tissue injury following ischemic insult (Jarald *et al*., 2008). Increased oxidative stress and reduce antioxidative ability in diabetes results in glomerular sclerosis, renal tubular injury, proteinuria and leads to gradual loss of renal function (Shah *et al*., 2007). Moreover, hyperlipidemia predicts progressive loss of renal function in chronic kidney disease in both type 1 and type 2 diabetes (Earle *et al*., 2008). Recent evidence demonstrates that chronic hypoxia of the tubulointerstitium has a pathogenic role in diabetic nephropathy (Singh *et al*., 2008). Diabetic rats had higher values of plasma BUN than control rats (Shou-Chieh *et al*., 2009).

Feeding diabetic rats with the supplemented diet with the three different levels (5, 10 and 15%) of hazelnut had lower food intake values and higher body weight gain as compared to untreated diabetic groups which were more detectable with increasing hazelnut level. These results may be attributed to the higher caloric content of supplemented diet with hazelnut diet as compared to normal basal diet. Hazelnut is a rich source of monounsaturated fatty acids (Alasalvar *et al*., 2006) and polyunsaturated fatty acids (Feldman, 2002). The increase in fat content of the diet is responsible for satiety and increased total calories which in turn leads to lower ingestion by animals. These results agreed with Willett (1998) who showed that higher percentage of fat in the diet results in increased body weight. Mendoza *et al*. (2006) reported that the consumption of energy-dense foods is associated with weight gain and obesity. Administration of the three different levels of hazelnut significantly decreased blood glucose level and serum concentrations of TL, TG, TC, AST, ALT, UN, UA and Cr and significant increase in serum level of insulin, TSH, FSH and LH compared to the diabetic control rats.

The mechanism by which hazelnut improved blood glucose level and serum concentrations of the mentioned parameters may be related to its antioxidant activity. It contains antioxidants constituents such as vitamin E and phenolic components, folic acid and L-arginine (Brown and Hu, 2001). Therefore, antioxidants activity of hazelnut can have beneficial effect on pancreatic beta-cells by neutralizing the oxidative stress. Normal beta-cells compensate for insulin resistance by increasing glucose-stimulated insulin secretion or beta-cell mass (Kaneto *et al*., 2001).

Hazelnut is one of the rich sources of MUFA and PUFA which results in improvement in glycemia (Garg *et al*., 1988). Higher consumption of polyunsaturated fat was associated with lower fasting plasma concentrations of glucose (Trevisan *et al*., 1990) and is associated with a lower risk of type 2 diabetes (Salmeron *et al*., 2001). Moreover, hazelnut is an excellent source of soluble dietary fiber (Brown *et al*., 1999) which help manage blood glucose level (Anderson *et al*., 2009).

One of the most important functions of insulin is the modulation of blood FSH levels and the strong correlation have been found between FSH and insulin levels in blood plasma (Sudha *et al*., 1999). Insulin has essential role in maintenance of LH receptors on Leydig cells (Orth *et al*., 1979). Regarding the antioxidant effect, the effect of this plant on gonadal hormone levels of diabetic rats as a reproductive function is probably performed via inhibition of oxidative stress. Therefore, the improvement in blood glucose and serum insulin levels may be related to the improvement in serum TSH, FSH and LH hormones.

Regular nuts consumption in hypercholesterolemia results in significant reductions in TC and LDL-C (Tey *et al*., 2011) with some showing increases in HDL-C (Sheridan *et al*., 2007). In addition to MUFA, PUFA and phytosterols found in hazelnut have been reported to

reduce plasma total and LDL cholesterol concentrations (Feldman, 2002). Hazelnut is an excellent source of vitamin E (Alasalvar *et al*., 2003) which has been shown to reduce the risk of CHD (Rimm and Stampfer, 1997). This cardioprotective effect appears due to vitamin E-induced inhibition of LDL oxidation (Steinberg and Lewis, 1997). Whole nuts including hazelnut may provide a variety of non-fat cardioprotective constituents including arginine (Cooke and Tsao, 1997), copper (Klevay, 1993) and magnesium (Elin and Hosseini, 1993) which appears to have beneficial effects on vascular endothelial function (Brown and Hu, 2001). High beta-sitosterol and fiber content of a hazelnut-enriched diet may contribute to some extent to the observed changes in lipid and lipoprotein concentrations (Griel and Kris-Etherton, 2006).

The improvement in liver and kidney functions in treated diabetic rats with hazelnut may be related to the antioxidant properties of hazelnut which have scavenge free radicals and thereby may protect cells from oxidative stress. Hazelnut contains vitamin E (alpha-tocopherol isomer), phytosterols and polyphenols (Alasalvar *et al*., 2006) that is known as antioxidants and had strong free radical scavenging (Choi *et al*., 2002). The hypoglycemic and antioxidant prevent oxidative stress and preserve liver function was observed in diabetic rats (Eliza *et al*., 2009). This beneficial effect may have resulted primarily from the hypoglycemia potential of dietary antioxidant in diabetes (Bolkent *et al*., 2004). Recent observations have shown that many of complications in diabetic rats are diminished upon supplementation with certain dietary antioxidants such as flavonoids and polyphenols (Kishore *et al*., 2009).

Conclusions: The present results revealed that regular consumption of hazelnut may be benefits in reducing blood glucose level and serum concentration of TL, TG and TC as well as the improvement of liver and kidney functions. In addition to the improvement of TSH, FSH and LH in diabetic rats, however this explanation required more investigation.

REFERENCES

Alasalvar, C., F. Shahidi and K.R. Cadwallader, 2003. Comparison of natural and roasted Turkish Tombul hazelnut (*Corylus avellana* L.) volatiles and flavor by DHA/GC/MS and descriptive sensory analysis. J. Agric. Food Chem., 51: 5067-5072.

Alasalvar, C., J.S. Amaral and F. Shahidi, 2006. Functional lipid characteristics of Turkish Tombul hazelnut (Corylus avellana L.). J. Agric. Food Chem., 54: 10177-10183.

American Diabetes Association (ADA), 2007. Diagnosis and classification of diabetes mellitus. Diabetes Care, 30: 42-47.

Ana Angelica, H., F. Ethel, L.B. Ary and M.G. Cristiano, 2009. Effect of naringerin on biochemical parameters in the streptozotocin-induced diabetic rats. Brazilian Arch. Biol. Technol., 52: 51-59.

Anderson, J.W., P. Baird, R. Davis, S. Ferreri, M. Knudtson, A. Koraym, V. Waters and C.L. Williams, 2009. Health Benefit Dietary Fiber. Nutr. Rev., 67: 188-205.

Ballester, J., M.C. Munoz, J. Dominguez, M.J. Palomo, M., Rivera, T. Rigau, J.J. Guinovart and J.E. Rodríguez-Gil, 2007. Tungstate administration improves the sexual and reproductive function in female rats with streptozotocin-induced diabetes. Hum Reprod., 22: 2128-2135.

Bansal, V., J. Kalita and U.K. Misra, 2006. Diabetic neuropathy. Postgrad Med. J., 82: 95-100.

Bolkent, S., R. Yanardag, B.O. Karabulut and S.O. Ozsoy, 2004. The morphological and biochemical effects of glibornuride on rat in experimental diabetes. Human Exp. Toxicol., 23: 257-264.

Brown, L., B. Rosner, W.W. Willett and F.M. Sacks, 1999. Cholesterol-lowering effects of dietary fiber: A meta-analysis. Am. J. Clin. Nutr., 69: 30-42.

Brown, A.A. and F.B. Hu, 2001. Dietary modulation of endothelial function. Implications for cardiovascular disease. Am. J. Clin. Nutr., 73: 673-686.

Buko, V., O. Lukivskayam, V. Nikitin, Y. Tarasov, L. Zavodnik, A. Borodinsky and B. Gorenshtein, 1996. Hepatic and pancreatic effects of olyenoyl-phosphatidylcholine in rats with alloxan induced diabetes. Cell Biochem. Funct., 14: 131-137.

Carleton, H., 1979. Histological techniques. 4th Edn., London, Oxford University Press, New York, USA, Toronto, pp: 267.

Choi, C.W., S.C. Kim, S.S. Hwang, B.K. Choi, H.J. Ahn, M.Y. Lee, S.H. Park and S.K. Kim, 2002. Antioxidant activity and free radical scavenging capacity between Korean medicinal plants and flavonoids by assay-guided comparison. Plant Sci., 163: 1161-1168.

Cooke, J.P. and P.S. Tsao, 1997. Arginine: A new therapy for atherosclerosis? Circulation, 95: 311-312.

Daniel, R.S., K.S. Devi, K.T. Augusti and N.C. Sudhakaran, 2003. Mechanism of action of antiatherogenic and related effects of Ficus bengalensis Linn. Flavonoids in experimental animals. Indian J. Exp. Biol., 41: 296-303.

Earle, K.A., D. Harry and K. Zitouni, 2008. Circulating cholesterol as a modulator of risk for renal injury in patients with type 2 diabetes. Diabetes Res. Clin. Pract., 79: 68-73.

Elin, R.J. and J.M. Hosseini, 1993. Is the magnesium content of nuts a factor for coronary heart disease? Arch. Int. Med., 153: 779-780.

Eliza, P., S. Daisy and V. Ignacimuthu, 2009. Normoglycemic and hypolipidemic effect of costunolide isolated from Costus speciosus (Koen ex. Retz.) streptozotocin-induced diabetic rats. Chem. Biol. Interact, 179: 329-334.

Farombi, E.O. and O.O. Ige, 2007. Hypolipedemic and antioxidant effects of ethanolic extract from dried calyx of Hibiscus sabdariffa in alloxan-induced diabetic rats. Fundam Clin. Pharmacol., 21: 601-609.

Feldman, E.B., 2002. The scientific evidence for a beneficial health relationship between walnuts and coronary heart disease. J. Nutr., 132: 1062S-1101S.

Florkowski, C.M., 2002. Management of co-existing diabetes mellitus and dyslipidaemia: Defining the role of thiazolidinediones. Am. J. Cardio vasc Drugs, 2: 15-21.

Franz, M.J., J.P. Bantle, C.A. Beebe, J.D. Brunzell, J.L. Chiasson, A. Garg, L.A. Holzmeister, B. Hoogwerf, E. Mayer-Davis, A.D. Mooradian, J.Q. Purnell and Wheeler, 2002. Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. Diabetes Care, 25: 148-98.

Garg, A., A. Bonnie, S.M. Grundy, Z.J. Zhang and R.H. Unger, 1988. Comparison of a high-carbohydrate diet with a high-monounsaturated-fat diet in patients with non-insulin-dependent diabetes mellitus. N. Engl. J. Med., 319: 829-834.

Granner, D.K., 1996. Hormones of the pancreas and gastrointestinal tract. In: Murray, R.K., R.K. Granner, P.A. Mayes and V.W. Rodwell (Eds.), Harper's Biochemistry, 24th Edn., Appleton and Lange, Connecticut, USA, pp: 586-587.

Griel, A.E. and P.M. Kris-Etherton, 2006. Tree nuts and the lipid profile: A review of clinical studies. Br. J. Nutr., 96: S68-S78.

Hamden, K., S. Carreau, S. Lajmi, D. Aloulou, D. kchaou and A. Elfeki, 2008. Protective effect of 17"-estradiol on hyperglycemia, stress oxidant, liver dysfunction and histological changes induced by alloxan in male rat pancreas and liver, Steroids, 94: 495-501.

Hemalatha, S., A.K. Wahi, P.N. Singh and J.P. Chansouria, 2004. Hypoglycemic activity of Withania coagulans Dunal in streptozotocin-induced diabetic rats. J. Ethnopharmacol., 93: 261-264.

Jarald, E.E., S.B. Joshi and D.C. Jain, 2008. Antidiabetic activity of aqueous extract and non polysaccharide fraction of Cynodon dactylon Pers. Indian J. Exp. Biol., 46: 660-667.

Jenkins, D.J., J.M. Wong, C.W. Kendall, A. Esfahani, V.W. Ng, T.C. Leong, D.A. Faulkner, E. Vidgen, K.A. Greaves and G. Paul, 2009. The effect of a plant-based low carbohydrate ("Eco-Atkins") diet on body weight and blood lipid concentrations in hyperlipidemic subjects. Arch. Int. Med., 169: 1046-1054.

Jiang, G.Y., 1996. Practical Diabetes. 1st Edn., Beijing: People's Health Publishing House, pp: 295-296.

Kaneto, H., G. Xu, K.H. Song, K. Suxuma, S. Bonner-Weir, A. Sharma and G.C. Weir, 2001. Activation of the hexosamine pathway leads to deterioration of pancreatic â-cell function through the induction of oxidative stress. J. Biol. Chem., 276: 31099-31104.

Khaki, A., M. Nouri, F. Fathiazad, H.R. Ahmadi-Ashtiani, H . Rastgar and S. Rezazadeh, 2009. Protective effect of quercetin on spermatogenesis in streptozotocin-induced diabetic rat. J. Med. Plan., 8: 57-64.

Kishore, A., G.K. Nampurath, S.P. Mathew, R.T. Zachariah, B.K. Potu, M.S. Rao, M. Valiathan and M.R. Chamallamudi, 2009. Antidiabetic effect through islet cell protection in streptozotocin diabetes: A preliminary assessment of two thiazolidin-4-ones in Swiss albino mice, Chem. Biol. Interact, 177: 242-246.

Klevay, L.M., 1993. Copper in nuts may lower heart disease risk. Arch. Intern. Med., 153: 401-402.

Laxmi, V., K. Anirudh, K. Basant, K. Umesh and S. Rajesh, 2010. Antidiabetic activity of Cassia occidentalis (Linn) in normal and alloxan-induced diabetic rats. Indian J. Pharmacol., 42: 224-228.

Lyra, R., M. Oliveira, D. Lins and N. Cavalcanti, 2006. Prevention of type 2 diabetes mellitus. Arq. Bras. Endocrinol. Metabo., 50: 239-249.

Mallick, C., S. Mandal, B. Barik, A. Bhattacharya and D. Ghosh, 2007. Protection of testicular dysfunctions by MTEC, a formulated herbal drug, in streptozotocin induced diabetic rat. Biol. Pharm. Bull., 30: 84-90.

Marles, F.J. and N.R. Farnsworth, 1996. Antidiabetic plants and their active constituents: An update Protocol. J. Nat. Med., 85-111.

Medina, J. and R. Moreno-Otero, 2005. Pathophysiological basis for antioxidant therapy in chronic liver disease. Drugs, 65: 2445-2461.

Mendoza, J.A., A. Drewnowski, A. Cheadle and D.A. Christakis, 2006. Dietary energy density is associated with selected predictors of obesity in U.S. children. J. Nut., 136: 1318-1322.

Oksanen, A., 1975. Testicular lesions of streptozotocin diabetic rats. Horm Res., 6: 138-144.

Orth, J.M., F.T. Murray and C.W. Bardin, 1979. Ultrastructural changes in Leydig cells of streptozotocin-induced diabetic rats. Anat Rec., 195: 415-430.

Posario, P.W., 2010. Normal values of serum IGF-I in adults: Results from a Brazilian population. Arq. Bras. Endocrinol. Metabol., 45: 477-481.

Reeves, P.G., F.H. Nielson and G.C. Fahmy, 1993. Reports of the AmericanInstitute of Nutrition, adhoc-wiling committee on reformulation of the AIN Rodent diet. J. Nutr., 123: 1939-1951.

Rimm, E.B. and M.J. Stampfer, 1997. The role of antioxidants in preventive cardiology. Curr. Opin Cardiol., 12: 188-194.

Sabate, J., 2003. Nut consumption and body weight. Am. J. Clin. Nutr., 78: 647S-650S.

Sabate, J., K. Oda and E. Ros, 2010. Nut consumption and blood lipid levels: A pooled analysis of 25 intervention trials. Arch. Int. Med., 170: 821-827.

Salmeron, J., F.B. Hu and J.E. Manson, 2001. Dietary fat intake and risk of type 2 diabetes in women. Am. J. Clin. Nutr., 73: 1019-1026.

Shah, S.V., R. Baliga, M. Rajapurkar and V.A. Fonseca, 2007. Oxidants in chronic kidney disease. J. Am. Soc. Nephrol., 18: 16-28.

Sharma, S., A. Nasir, K. Parbhu, B. Mursy and G. Dev, 2003. Hypoglycemic and hypolipidemic effect of etanolic extract of seeds in alloxan induced diabetic rabbits. J. Ethnopharmacol., 85: 201.

Sheridan, M.J., J.N. Cooper, M. Erario and C.E. Cheifetz, 2007. Pistachio nut consumption and serum lipid levels. J. Am. College Nutr., 26: 141-148.

Shou-Chieh, W., L. Shiow-Fen, W. Chau-Jong, L. Chao-Hsin, L. Wen-Chin and L. Huei-Jane, 2009. Aqueous extract from hibiscus sabdariffa linnaeus ameliorate diabetic nephropathy via regulating oxidative status and Akt/Bad/14-3-3g in an Exp. Anim. Model eCAM, 4: 1-9.

Singh, D.K., P. Winocour and K. Farrington, 2008. Mechanisms of disease: The hypoxic tubular hypothesis of diabetic nephropathy. Nat. Clin. Pract Nephrol., 4: 216-226.

Steinberg, D. and A. Lewis, 1997. Oxidative modification of LDL and atherogenesis. Circulation, 95: 1062-1071.

Sudha, S., G. Valli, J.P. Mary, J. Arunakaran, P. Govindarajulu and K. Balasu-Bramanian, 1999. Influence of streptozotocin-induced diabetes and insulin treatment on the pituitary-testicular axis during sexual maturation in rat. Endocrinol. Diabetes, 107: 14-20.

Tey, S.L., R.C. Brown, A.W. Chisholm, C.M. Delahunty, A.R. Gray and S.M. Williams, 2011. Effects of different forms of hazelnuts on blood lipids and α-tocopherol concentrations in mildly hypercholesterolemic individuals. Eur. J. Clin. Nutr., 65: 117-124.

Trevisan, M., CV. Krogh, J. Freudenheim, A. Blake, P. Muti, S. Panico, E. Farinaro, M. Mancini, A. Menotti and G. Ricci, 1990. Consumption of olive oil butter and vegetable oils and coronary heart disease risk factors: The Research Group ATS-RF2 of the Italian National Research Council. JAMA., 263: 688-692.

Uladimir, O.M., 2003. Coronary risk factor. J. Diabet. Assoc. India, 29: 3-8.

Weststrate, J.A. and G.W. Meijer, 1998. Plant sterol-enriched margarines and reduction of plasma total- and LDL-cholesterol concentrations in normo-cholesterolaemic and mildly hypercholesterolaemic subjects. Eur. J. Clin. Nutr., 52: 334-343.

Willett, W.C., 1998. Is dietary fat a major determinant of body fat? Am. J. Clin. Nutr., 67: 556-562.

Young, D.S., 2001. Effects of disease on clinical Lab. tests, 4th Edn., AACC.