

Role of Dietary Fibers in the Management of Diabetes Induced Heart Disease in Male Rats

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Abstract: The present study was conducted to evaluate the effect of oat or wheat bran (as a source of dietary fibers) on the heart disease associated with streptozotocin (STZ)-induced diabetes in male rats. As a result of induction of diabetes, the level of serum glucose and lipids (total lipids, triglycerides, total cholesterol, LDL-C, vLDL-C), as well as activity of lactic dehydrogenase (LDH) and creatinine kinase (CK) were increased, while HDL-C level was decreased. This goes in parallel with a significant reduction in the level of serum insulin and T-homocystein (tHcy). Furthermore, a reduction of total protein and glycogen content in the heart of diabetic rats were recorded. In addition, the diabetic rats exhibited marked trend for increased malondialdehyde and protein carbonyl levels, accompanied with decreased glutathione content in the heart tissue, which together with the other reported abnormalities predict development of heart disease as a result of diabetes. In contrast, feeding diabetic rats on diets supplemented with 7% oat or wheat bran was found to be effective in the management of diabetes-induced changes with the greatest effect being achieved with oat bran administration. Thus, it can be concluded that diet high in plant fibers, particularly oat bran is useful in reducing the development of heart disease associated with diabetes.

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1. Introduction:

Diabetes mellitus is frequently associated with heart disease that represents one of the most prevalent causes of death worldwide (Sarafidis *et al.*, 2005). Several risk factors, including hyperglycemia, insulin lack, insulin resistance and lipid abnormalities seemed to play a major role in the etiology of this disease (De Fronzo and Ferrannini, 1991). Recent research reveals that dietary modification such as increasing intake of plant fiber can improve insulin sensitivity, glucose tolerance and other metabolic disturbances associated with diabetes (Galisteo *et al.*, 2008).

Dietary fiber is a collective term for a variety of plant substances that are resistant to digestion by human gastrointestinal enzymes (John *et al.*, 2004). Since they are not absorbed into the body, dietary fibers are not a nutrient. Dietary fibers can be classified as either water soluble or insoluble, based on its ability to hold water and swell or not (Galisteo *et al.*, 2008). The structural or non viscous fibers (lignin, cellulose and some hemicellulose) are water insoluble. Vegetables, cereals and grains are especially rich in water insoluble fiber, with the highest amount found in wheat and corn. Water-insoluble fiber is responsible for increased stool bulk and help to regulate bowel movements. The natural gel-forming or viscous fibers (pectins, gums, mucilages, algal polysaccharides, some

polysaccharides and some hemicelluloses) are water soluble. Food rich in water-soluble fibers are dried beans, barely, oats, and some fruits and vegetables (Anderson *et al.*, 1990). Of total dietary fiber intake, approximately 20% is water soluble and 80% is water insoluble (Bazzano *et al.*, 2003). Studies in this field have postulated that high intake of unrefined cereals (rich in insoluble type) is beneficial in relation to non-infectious diseases, such as gastrointestinal problems and certain cancers, especially that of large bowel (Chatenoud *et al.*, 1998). Science then, numerous studies indicated that increased consumption of both types of dietary fibers is effective in preventing or treating chronic diseases, including heart disease and diabetes (Venn and Mann, 2004). Results of other studies recommended insoluble dietary fiber as a way of reducing food intake, body weight, and obesity (Olmo *et al.*, 2007), as well as ameliorating hyperlipidemia and other cardiovascular risk factors (Jacobs *et al.*,). It was also demonstrated that high intake of soluble dietary fiber help to reduce total cholesterol, LDL-C and thereby the risk of heart disease among normal and hyperlipidaemic subjects (Mälkki, 2001). Other epidemiologic studies linked increased consumption of dietary fiber with reduced incidence of diabetes (Meyer *et al.*, 2000). In the same way, some experimental studies indicated that soluble dietary fibers can improve blood glucose and decrease body's

need to insulin (Casiraghi *et al.*, 2006). The related mechanism may be enhanced insulin sensitivity (Ylonen *et al.*, 2003) and decreasing insulin resistance (Temple *et al.*, 1992) In the light of these findings, the present study was undertaken to evaluate whether prolonged intake (3 months) of diet rich in two types of plant fibers could play a positive role in reducing development of heart disease associated with diabetes. The selected approach was to use two types of plant products, oat bran (as a source of soluble fiber) and wheat bran (as a source of insoluble fiber) to compare their effects in this context.

2. Materials and Methods

1- Materials

A- Experimental animals:

Sixty (60) male albino rats (*Rattus rattus*) weighing from 130-150 g were used in the present study. They were obtained from Helwan Animal Farm, Cairo, Egypt. Animals were kept under good ventilation and received a balanced diet and water *ad libitum*. They were acclimated to laboratory conditions for 2 weeks prior to experimentation.

B- Chemicals:

Streptozotecin (STZ) was obtained from Sigma Company, Egypt. All other reagents were purchased from El-Gomhoria Co., Egypt; and all the reagents were of analytical grade.

C-Plant Fibers:

Wheat bran (as a source of insoluble fiber) and oat bran (as a source of soluble fiber) were obtained from local market, Mansoura city, Egypt.

D- Induction of diabetes:

At the start of the experiment, diabetes was induced by interperitoneal injection of (STZ) to overnight fasted rats. STZ was applied as a single freshly prepared dose (50 mg/ kg b.wt) dissolved in citrate buffer PH 4.4 (Nandini *et al.*, 2000). Successful induction of diabetes was assessed 3 days after STZ injection by performing glucose urine analysis, using glucokotest obtained from Condor-Teco Technology Co.Ltd Netherland for *in vitro* analysis.

E- Experimental diet:

The control group was fed a standard normolipidemic diet consisting of protein 21%, fat 3.2% and fibers 3.44%, according to The Nutrient Requirements of Laboratory Animals (1995).

F- Animal grouping

The rats were divided into six groups; each of 6 rats, the first group was maintained untreated and served as a control animal. The second and third groups received diet supplemented with 7% of wheat bran or oat bran, respectively as described by Cameron-Smith *et al.* (1997). The fourth group is diabetic untreated animals. The fifth and six groups are

diabetic animals given diets supplemented with wheat bran or oat bran at the same dose as described in the second and third groups.

At the end of the experimental period (3 months), animals were overnight fasted and sacrificed under ether anesthesia. Blood was collected in non-heparinized centrifuge tube, and centrifuged for 15 minutes at 860 G. Non hemolized sera were separated and kept at -20C for further analysis. Thereafter, liver and heart specimens were removed, weighed and homogenized for later biochemical measurements. Other specimens of liver and heart were weighed and kept in trichloroacetic acid solution (TCA) for determination of glycogen content.

2- Methods

Estimated parameters:

Levels of glucose and lipid profile (total cholesterol (TC), triglycerides (TG) and HDL-C) were estimated using colorimetric kits purchased from Spinreact CO., Spain, as described by McCleary and Codd (1991). and Young (1995) respectively. Liver glycogen content was determined as described by (Nicholas *et al.*, 1956), while reduced glutathione (GSH) was estimated according to the method of Prins and Loose (1969). Total lipids (T.lipids) and total protein (T.protein) were estimated using kits from diamond diagnostic, Cairo, Egypt according to the methods of Henry (1964) and Frings *et al* (1972), respectively. Serum insulin level was estimated using IMMULITE/IMMUULITE 1000 analyzer, according to the method of Chevenne *et al.*, (1998).. LDL-C and VLDL-C concentrations in serum was calculated according to the formula applied by Friedewald *et al.* (1972), while the atherogenic index (AI) was calculated according to the equation described by Pandya *et al.* (2006).

The activity of creatinine kinase (CK) was estimated using kinetic kit from Elitech, Division de SEPPIMS. A Zone Industrielle, France, while lactic dehydrogenase (LDH) activity was estimated using kinetic kit from Humman, Gesellschaft for biochemical and diagnostica, Wiesbaden Germany, according to Young (1995) and Witt and Trendelenburg (1982), respectively. The level of malondialdehyde (MDA) (the end product of lipid peroxidation) was determined as a thiobarbituric acid reactive substance (TBAR) according to a modification of the method of Ohkawa *et al.* (1982), while protein carbonyl (PC) content was measured as described by Smith *et al.* (1991). Serum total homocysteine (tHcy) concentration was measured using IMMULITE/IMMUULITE 1000 analyzer, according to method of Bastom and Lathrop (1997).

3- Statistical analysis:

In the present study, obtained results were analyzed by One Way ANOVA (analysis of variance) test and post comparison was carried out with Tukey test. The results were expressed as means \pm standard error (SE). The criterion for statistical significance was $p < 0.05$ (Snedecor and Cochran, 1982).

3. Results:

In the present study, diabetic rats exhibited significant ($P < 0.05$) increase in the serum glucose and lipids (TL, TC, TG, LDL-C, vLDL-C), whereas serum levels of insulin, HDL-C, and tHcy showed significant reduction (Table 1). Similarly, the present results showed significant reduction in CK and LDH activities, accompanied with significant ($P < 0.05$) increase in MDA and PC levels in heart tissues of diabetic rats, but reduction in total protein, glycogen and GSH in both liver and heart tissues of diabetic rats was also noticed (Table 2, 3).

On the other hand, feeding diabetic rats on diet supplemented with (7 % oat bran or wheat bran) helped to produce beneficial effects, which seemed of significant ($P < 0.05$) value for all tested parameters, including insulin, glucose, lipids, total protein, tHcy, CK, LDH and oxidative stress markers. However, the oat bran supplementation recorded higher effect than wheat bran.

Besides, dietary fibers supplementation exhibited similar benefits, regarding their effects on non-diabetic rats when compared with normal control rats. Thus, it could be concluded that dietary fibers, particularly oat type have favorable health advantages for both normal and diabetic cases.

4. Discussion:

A large number of studies in human and experimental animals have evidenced the association between diabetes mellitus and development of cardiac disease (Richard *et al.*, 2010). The characteristic metabolic disturbances (hyperglycemia and dislipidemia) seen in diabetes are considered the most common risk factors for developing this disease. The causes for these metabolic disturbances and the management approaches to reduce the associated cardiac disorders are the subject of this work.

STZ-induced diabetes is a well documented model of experimental type I diabetes. In the present study, STZ injected rats exhibited abnormal metabolic pattern, characterized by increased serum levels of glucose with reduced insulin concentration, indicating their diabetic state. Other studies have confirmed these effects and further indicated that both hyperglycemia and lowered insulin levels being linked to the pathogenesis of heart disease in diabetes (Andallu and Vardacharyulu, 2001). Insulin makes it

possible for most body tissues to remove glucose from blood for use as fuel, for conversion to other needed molecules or for conversion into glycogen to be stored in liver and muscle cells. Lowered insulin levels result in the reverse conversion of glycogen to glucose with consequent decrease in glycogen accumulation. This could explain the decreased ability of diabetic tissues to accumulate glycogen, as seen in this study and other diabetic states (Bamri-Ezzine *et al.*, 2003). Decreased glycogen accumulation in the diabetic tissues may be an indication of impaired energy reserves coupled with reduced functional capacity (Carley and Severson, 2005). Therefore, the present finding of decreased glycogen levels in the diabetic heart can be considered as a marker for developing heart dysfunction consequent to induction of diabetes. In this context, other studies suggested a direct association between hyperglycemia and deleterious changes in diabetic myocardium, including myocytes hypertrophy, vascular fibrosis and increased collagen deposition (Fiordaliso *et al.*, 2004). These changes are likely a result of hyperglycemia-induced non enzymatic protein glycation, with accumulation of advanced glycation end products (AGES) in the myocardium, which may alter cellular function. Apart from the role of hyperglycemia, the increased lipid profile is also so prominent during diabetes that has suggested to be a major risk factor predisposing diabetic patients to develop heart disease. Increased lipids in diabetes may result from increased mobilization of fatty acids from peripheral deposits, which is mainly attributed to insulin deficiency, since insulin normally inhibits lipolysis (Al-Shamaony *et al.*, 1994). In this context, it was evidenced that the increased level of T.cholesterol is frequently developed in different diabetic states (EL-Wakf, 1997; EL-Wakf *et al.*, 1997). Several studies indicated that people with diabetes compared to non-diabetic persons often has high cholesterol levels. In diabetes, the increased cholesterol is possibly resulting from decreased level of HDL-C, together with increased LDL-C concentrations (Kesavulu *et al.*, 2001).

As reported earlier, LDL-C is the major cholesterol carrier in the blood, about 60-80% of cholesterol is carried by LDL-C (Ruzaidia *et al.*, 2004). Some of cholesterol is used by tissue and others returned to liver (Quinet *et al.*, 2009), but if there is much LDL-C in blood, cholesterol may be deposited. On the other hand, HDL-C picks up cholesterol and take it back to liver for reprocessing or excretion by a pathway called reverse cholesterol transport. Consequently, decreased HDL-C is associated with decreased cholesterol removal from extra hepatic tissues and increased risk of developing

cardiovascular disorders. HDL-C is, therefore, recognized as a factor that protects against development of atherosclerotic disease and thus increased HDL-C is associated with a decrease in coronary heart disease (Gao and Yuan, 2010). In contrast, high levels of both T.cholesterol and LDL-C are considered as major coronary risk factor through enhancing atherosclerosis (Rizzo *et al.*, 2009). Based on this, the present findings of increased T.cholesterol, LDL-C and atherogenic index (AI), with decreased HDL-C concentrations can be considered as indication for enhanced atherosclerosis with further cardiac injury as a result of diabetes. Beside this, high levels of triglycerides and vLDL-C have also been detected under present diabetic state which may be attributed to lack of insulin levels. Normally, insulin acts to activate the enzyme lipoprotein lipase, being responsible for

catalyzing breakdown of triglyceride rich lipoproteins (vLDL-C and chylomicrones) (de Vries *et al.*, 2003). Thereby, insulin lack impairs the normal insulin mediated activation of lipoprotein lipase, which result in over production of vLDL-C and leads to increased plasma triglycerides. In this way, increased triglycerides are subsequently associated with an increase of myocardial disorders. Regarding this, it seems reasonable to predict development of cardiac disorders under present diabetic status, characterized by elevation in both triglycerides and VLDL-C, as in agreement with other data indicating that increased intramyocarial triglycerides content in patients with diabetes may cause lipotoxicity and cardiomyocyte apoptosis that ultimately leads to cardiac dysfunction (Witteles *et al.*, 2008).

Table (1): Serum biochemical parameters in control and different treated rat groups.

Animal groups Parameters	Control	Wheat bran	Oat bran	Diabetic	Diabetic + wheat bran	Diabetic + oat bran
Glucose (mg/dl)	89.38 ±1.88	89.33 ±3.04	86.08 ±2.88	457.46 ±19.07 ^a	182.83 ±4.98 ^{ab}	150.7 ±4.29 ^{ab}
Insulin (µIU/dl)	3.42 ±0.12	3.43 ±0.11	3.65 ±0.09	1.17 ±0.09 ^a	2.18 ±0.08 ^{ab}	2.39 ±0.08 ^{ab}
T. lipid (mg/dl)	554.94 ±1.85	539.59 ±2.45	518.26±1.91 ^a	816.15±1.91 ^a	642.23 ±4.01 ^{ab}	604.30 ±4.38 ^{abc}
TC (mg/dl)	89.5 ±0.86	84.70 ±0.96	82.15 ±0.89 ^a	121.24 ±0.72 ^a	111.66 ±0.88 ^{ab}	105.15 ±0.72 ^{abc}
TG (mg/dl)	95.69 ±1.44	89.37 ±0.90 ^a	84.93 ±1.40 ^a	136.16 ±1.54 ^a	124.27 ±1.34 ^{ab}	115.93 ±1.59 ^{abc}
HDL-C (mg/dl)	38.66 0.51	40.31 ±0.69	43.80 ±0.26 ^a	24.73 ±0.64 ^a	28.59 ±0.56 ^{ab}	29.45 ±0.69 ^{ab}
LDL-C (mg/dl)	31.70 ±0.51	26.51 ±0.69	21.36 ±0.26 ^a	69.27 ±0.64 ^a	58.21 ±0.56 ^{ab}	52.51 ±0.69 ^{abc}
VLDL-C (mg/dl)	20.17 ±0.99	17.87 ±0.18 ^a	16.98 ±0.28 ^a	27.23 ±0.31 ^a	24.85 ±0.27 ^{ab}	23.19 ±0.32 ^{ab}
AI	1.33 0.59±	1.10 ±0.68 ^a	0.87 ±0.42 ^a	4.99 ±0.67 ^a	2.90 ±0.60 ^{ab}	2.57 ±0.62 ^{abc}
T. protein (g/dl)	5.10 ±0.11	5.44 ±0.17	6.07 ±0.10 ^a	2.79 ±0.09 ^a	3.56 ±0.12 ^{ab}	3.94 ±0.05 ^{ab}
tHcy (mg/dl)	12.81 ±0.34	15.06 ±0.28	14.47 ±0.43	5.45 ±0.29 ^a	8.15 ±0.25 ^{ab}	9.46 ±0.31 ^{ab}
CK (U/L)	229.2 ±4.57	210.14 ±2.47	206.57 ±2.77	481.77 ±11.49 ^a	382.34 ±4.07 ^{ab}	331.36 ±6.68 ^{abc}
LDH (U/L)	438.14 ±4.25	378.44 ±10.54 ^a	336.22 ±6.29 ^a	672.55 ±8.12 ^a	544.11 ±3.71 ^{ab}	508.95 ±3.53 ^{abc}

All values are expressed as mean ±SE of 6 animals.

^a Significant (P<0.05) on comparing with the control group.

^b Significant (P<0.05) on comparing with the diabetic group.

^c Significant (P<0.05) on comparing diabetic oat with diabetic wheat.

Table (2): Heart biochemical parameters and oxidative biomarkers in control and different treated rat groups.

Animal groups Parameters	Control	Wheat bran	Oat bran	Diabetic	Diabetic + wheat bran	Diabetic + oat bran
Glycogen (mg/g wet tissue)	59.74 ±0.95	69.93 ±0.3 ^a	72.88 ±1.17 ^a	24.46 ±2.12 ^a	32.62 ±1.06 ^{ab}	40.73 ±0.95 ^{ab a&b}
T. lipids (mg/g wet tissue)	331.56 ±3.51	321.75 ±2.29	297.24 ±5.36 ^a	555.23 ±3.63 ^a	395.39 ±9.11 ^{ab}	356.73 ±2.6 ^{abc}
TC (mg/g wet tissue)	50.66 ±1.85	47.52 ±2.45	42.91 ±1.91 ^a	75.90 ±1.91 ^a	64.52 ±4.0 ^{ab}	59.35 ±0.9 ^{abc}
TG (mg/g wet tissue)	42.18 ±0.83	38.43 ±1.55	34.69 ±1.13 ^a	61.32 ±0.87 ^a	52.61 ±0.70 ^{ab}	49.03 ±0.76 ^{ab}
T.protein (mg/g wet tissue)	2.91 ±0.026	3.03 ±0.029	3.18 ±0.035 ^a	1.06 ±0.019 ^a	2.18 ±0.011 ^{ab}	2.37 ±0.02 ^{abc}
CK (mg/g wet tissue)	361.38 ±5.77	375.69 ±2.10	364.33 ±1.71 ^a	130.43 ±3.80 ^a	171.64 ±4.15 ^{ab}	191.28 ±4.25 ^{abc}
LDH (mg/g wet tissue)	428.60 ±3.29	434.57 ±2.46 ^a	57.484 ±2.46 ^a	253.42 ±4.23 ^a	312.63 ±3.14 ^{ab}	337.71 ±4.09 ^{abc}
MDA (nmol/ g wet tissue)	143.13	135.31	129.63 ±1.57 ^a	415.06 ±2.51 ^a	291.77 ±2.45 ^{ab}	249.26 ±1.93 ^{abc}
PC (μ mol DNPH/ mg wet	0.44 ±0.02	0.36 ±0.014 ^a	0.31 ±0.016 ^a	0.82 ±0.015 ^a	0.63 ±0.012 ^{ab}	0.57 ±0.018 ^{ab}
GSH (mg/g wet tissue)	0.26 ±0.009	0.31 ±0.011 ^a	0.33 ±0.012 ^a	0.12 ±0.005 ^a	0.18 ±0.007 ^{ab}	0.21 ±0.21 ^{ab}

All values are expressed as mean ±SE of 6 animals.

^a Significant (P<0.05) on comparing with the control group.

^b Significant (P<0.05) on comparing with the diabetic group.

^c Significant (P<0.05) on comparing diabetic oat with diabetic wheat.

Table (3): Liver biochemical parameters and oxidative biomarkers in control and different treated rat groups.

Animal groups Parameters	Control	Wheat bran	Oat bran	Diabetic	Diabetic + wheat bran	Diabetic + oat bran
Glycogen (mg/g wet tissue)	99.39 ±1.56	103.75 ±1.49	106.3 ±1.97	40.46 ±1.73 ^a	73.65 ±1.71 ^{ab}	83.39 ±1.75 ^{abc}
T. lipids (mg/g wet tissue)	644.62 ±3.65	621.16 ±4.78 ^a	580.77 ±6.33 ^a	874.66 ±5.15 ^a	735.90 ±2.39 ^{ab}	692.65 ±1.77 ^{abc}
TC (mg/g wet tissue)	169.32 ±1.20	152.30 ±2.13 ^a	139.36 ±1.34 ^a	214.76 ±1.54 ^a	202.66 ±1.41 ^{ab}	190.52 ±1.48 ^{abc}
TG (mg/g wet tissue)	130.84 ±5.56	130.92 ±1.50	119.45 ±3.38	181.70 ±1.32 ^a	162.83 ±1.69 ^{ab}	151.63 ±3.59 ^{ab}
T. protein (mg/g wet tissue)	3.90 ±0.025	4.07 ±0.019 ^a	4.16 ±0.014 ^a	2.07 ±0.035 ^a	3.11 ±0.013 ^{ab}	3.32 ±0.018 ^{abc}
MDA (nmol/g wet tissue)	279.13 ±2.48	261.78 ±3.08 ^a	241.14 ±4.83 ^a	672.68 ±3.72 ^a	484.06 ±3.21 ^{ab}	440.30 ±3.20 ^{abc}
PC (μmolDNPH/ mg wet tissue)	0.63 ±0.015	0.59 ±0.009	0.52 ±0.01 ^a	0.93 ±0.016 ^a	0.82 ±0.008 ^{ab}	0.79 ±0.009 ^{ab}
GSH (mg/g wet tissue)	0.28 ±0.01	0.31 ±0.01	0.36 ±0.02 ^a	0.11 ±0.09 ^a	0.19 ±0.006 ^{ab}	0.20 ±0.006 ^{ab}

All values are expressed as mean ±SE of 6 animals.

^a Significant (P<0.05) on comparing with the control group.

^b Significant (P<0.05) on comparing with the diabetic group.

^c Significant (P<0.05) on comparing diabetic oat with diabetic wheat.

In searching for other (non lipid) factors responsible for incidence of cardiac disease in diabetes, special attention has been paid to the role of homocysteine. Homocysteine (Hcy) is thiol, non protein amino acid, not present in food, but generated from the essential amino acid methionine (Jacob *et al.*, 1998). Studies concerning Hcy in the diabetic patients have revealed either elevated (George *et al.*, 2004), or decreased (Wald *et al.*, 2002) Hcy levels. This contradiction could be related to changes in insulin concentration. Patients with insulin resistance syndrome showed elevated levels of plasma Hcy (Sheu *et al.*, 2000). Similarly, type II diabetic patients who have preserved pancreatic β -cells function and who are hyperinsulinemic, but insulin resistant have high Hcy concentration (Drzewoski *et al.*, 2000). However, the same patients when lose their β -cells reserve show a decline in Hcy concentration. On the other hand, type I diabetic patients, who are insulinopenic, have low Hcy levels (Cotellessa *et al.*, 2001). Analysis of the present results, revealed similar reduction in serum Hcy level as a result of diabetes, and further indicated that insulin lack observed in this study could be of help in explaining this finding, since insulin acts primary to stimulate uptake of amino acids, such as methionine which in turn can be converted to Hcy, thus increasing Hcy levels. In other way, decreased Hcy level may be contributed to impaired Hcy disposal pathway due to kidney dysfunction induced by diabetes, as kidney has important role in Hcy elimination. Normally, plasma Hcy has free and protein bound forms. Increased protein loss due to kidney dysfunction may cause decrease in protein bound fraction of Hcy (Ueland *et al.*, 1996). Since only the free fraction of total plasma Hcy should be filtered, which corresponds to approximately 70% of the total Hcy in rats (House *et al.*, 1998), the excessive protein loss in diabetes may cause acceleration of Hcy elimination with reduced Hcy levels (McKeever *et al.*, 1991). Therefore, the decreased serum protein concentration, as seen in this study could be considered as one mechanism for the lowering influence of diabetes on Hcy levels.

In this line, a number of recent studies have considered Hcy as an independent risk factor for the development of cardiovascular disorders in diabetes. Several mechanisms are suggested to be involved, among them is the increased oxidative stress as a result of Hcy alterations. The explanations is that Hcy can be broken down in healthy individuals into other thiol amino acids, such as cystein (Langman, 1999) which is considered as important rate limiting precursor for synthesis of the tripeptide glutathione (GSH) (Kidd, 1997). Homocysteine, cystein and GSH are the major amino thiols in human plasma,

which interact through disulphide exchange reactions (Ciek *et al.*, 2004). Alterations of any of these three thiols can therefore, affect the others. So, it seems responsible that decreased Hcy level recognized in diabetes may be linked to GSH depletions, as seen in this diabetic state and in other cases ((Ueland *et al.*, 1996). GSH is one of the most important non-enzymatic antioxidants in the cells and its depletion could lead to enhanced production of oxygen free radicals with increased oxidative stress (Bansal and Bilaspuri, 2010). It follows that reduction in both Hcy and GSH levels can cause a state of oxidative stress.

Oxidative stress has been suggested to play a major role in the pathogenesis of many diabetic complications (EL-Wakf, 1996). Oxidative stress is defined as a shift in the balance of cellular oxidation-reduction reactions in favor of oxidation, which leads to damage of the cells and formation of molecular products that are indicative of oxidative stress, such as protein carbonyl (PC) and malonaldehyde (MDA) products (Bhor *et al.*, 2004). Excessive production of these toxic species may cause cellular membrane damage, with subsequent alteration in cellular functions. In this context, several blood enzymes have shown to be indicative of cell damage with increasing cell membrane permeability. These enzymes become recognizable in the serum, presumably by leakage through diseased or damaged tissues with altered membrane permeability. Creatine kinase (CK) and lactate dehydrogenase (LDH) are energetic enzymes, which prominently present in cardiac tissue and can be used to assess heart injury or disease (Meas *et al.*, 2009). Therefore, the present finding of increased serum activities of both CK and LDH with decreased cardiac activity of these enzymes can be considered as indicator for myocardial damage, as evidenced here by the increased accumulation of both PC and MDA in the cardiac tissue of diabetic rats.

Considering these alterations, together with other variables potentially related to risk of cardiac disease in diabetes, efforts continue to the find suitable therapeutic approaches. The inability of clinical trials to find satisfactory approaches has led to a shift towards alternative forms of therapy derived from plants or plant products. In this respect, dietary plant fibers are considered as a functional food, i.e a food with health benefits. In the field of diabetes research, it was indicated that use of plant fibers, mainly soluble type from psyllium (Brown *et al.*, 1999), guar gum (Anderson *et al.*, 1991) and oat bran (Jenkins *et al.*, 2002) is beneficial in the control of metabolic disturbances being involved in the pathogenesis of most diabetic complications, including heart disease (Jacobs *et al.*, 2000). In accord, the present study evidenced that feeding

diabetic rats on diet supplemented with oat bran (rich in soluble fiber) has shown lowered diabetic hazards. This was observed mainly in terms of improving glucose, insulin and lipids, as well as oxidative stress markers, which may contribute to improved cardiac status as assessed here by the normalized cardiac biomarkers, CK and LDH. Such an effect was also found on feeding diabetic rats on wheat bran-diet (rich in insoluble fiber), however wheat bran was not as effective as oat bran. In this way, the present study have shown that diets rich in oat or wheat fibers are beneficial for reducing diabetes and associated cardiac alterations, with the most potential action being attained with oat bran fiber. The reason for this difference may be related to the type of consumed fibers being soluble or insoluble. The followings are specific properties for each fiber type which may help to understand their different actions.

In terms of soluble fibers, predominantly oat bran, several studies have evidenced the efficiency of this fiber type to normalize blood glucose and insulin levels. Oats soluble fiber comprise a class of non-digestible polysaccharides known as β -glucans that are found widely in barely, yeast, bacteria, algae, mushrooms and oats (Madhujith and Shahidi, 2007). The percentage of β -glucans in various oat products are: oat bran about 5.5 %, while rolled oats and whole flour, about 4 % (Pick *et al.*, 1996). Oat β -glucan was reported to have glucose regulating activity, that may be related to the ability of soluble fiber types to hold water and swell, resulting in highly viscous gastric contents that may delay gastric emptying and/or intestinal absorption. Thereby, reduce postprandial glucose levels and improve insulin sensitivity in both diabetic and non-diabetic persons (Sierra *et al.*, 2002). It also favors increasing glucose uptake into skeletal muscles by increasing muscles content of insulin-responsive glucose transporter type 4 (GLUT-4) (Song *et al.*, 2000). Soluble fibers may also affect secretion of gut hormones or peptides, such as cholecystokinin (CCK) or glucagon-like peptide-1 (GLP-1), independent of glycemic response, which may act as satiety factors or alter glucose hemostasis. However, the control of blood glucose levels can't attribute only to soluble fibers. Although insoluble fibers are mainly non viscous and have negligible effects on postprandial glucose responses and only small effect on macronutrient absorption (Galisteo *et al.*, 2008), surprisingly, most epidemiological studies clearly showed that increased consumption of mainly insoluble cereal fibers and whole grains has been recommended to improve whole-body insulin sensitivity (Weickert *et al.*, 2006), and to lower serum glucose concentrations (Wolever *et al.*, 1992). An effect that was associated with earlier increase of postprandial active values of

the glucose-dependant insulin tropic polypeptide (GIP) (Asmar *et al.*, 2010), which inturn may represent a mechanism for controlling glucose and risk of diabetes. It was also reported that insoluble fibers predominantly from wheat bran is a source of magnesium (Jenkins *et al.*, 1975). Decreased magnesium was associated with insulin resistance, and magnesium supplementation was found to improve glucose handling (Brown *et al.*, 1999). Thus, wheat bran may affect glucose homeostasis and risk of diabetes indirectly through high presence of micronutrients, such as magnesium.

Apart from this gluco-metabolic regulation, numerous clinical and animal studies have indicated improved lipid metabolism following intake of dietary fibers, mainly soluble type (Ludwig *et al.*, 1999). In particular, consumption of soluble fiber from oat products was found to decrease blood concentration of cholesterol, especially low density lipoprotein (LDL-C) among hypercholesterolemic patients (Ripsin *et al.*, 1992). Other investigators also described a significant reduction of plasma triglyceride concentrations following prolonged intake of diets with high soluble fiber contents. The major mechanism involved in the hypocholesterolemic effect of soluble fiber (most often consumed as β -glucan from oat) is mediated by increased excretion of bile acids which might explain its cholesterol lowering activity (Sayar *et al.*, 2006). Concerning the hypotriglyceridemic effect, it is consistent with a possible delay in the absorption of triglycerides from the small intestine (John *et al.*, 2004). However, other authors have related this effect to the fact that soluble fiber from different sources, such as oat barn might decrease VLDL-C synthesis rate and accelerate VLDL-C removal with subsequent lowering of plasma triglyceride. This hypolipidemic action of soluble fiber intake was similarly demonstrated following consumption of different sources of insoluble fibers, but in less pronounced way, as evidenced in the present study. In support, a comparative study also showed this effect by the finding that oat bran has an advantage over wheat bran in lowering serum lipids when tested on large number of individuals with initial mean serum cholesterol concentrations above the desirable range (Lia *et al.*, 1995). To date, no obvious mechanisms have been provided for the hypolipidemic action of wheat bran. However, almost studies on such wheat bran effect have focused on the role of insoluble fiber-lignin. Lignin constitute about 3 % of the weight of wheat bran (Mongeau and Brassad, 1982) that has shown to bind bile acids and reduce serum cholesterol (Kritchevsky and Story, 1974). Other studies have researched the impact of wheat protein-gluten. About 14% of the weight of wheat bran or 27

% of its energy content is protein (McCance and Widdowsoo, 1992). Studies with increased wheat bran intake may therefore increase protein intake. In particular, high protein-high fiber intake was found to increase bile acid loss in human (Cummings *et al.*, 1979), and hence reduce cholesterol level (Jenkins *et al.*, 2002). In previous metabolic study, an exchange of approximately 10 % of daily energy from carbohydrate to wheat-gluten resulted in a 13 % reduction in triglycerides (Salmeron *et al.*, 1997). It is possible that the reduction in triglycerides was the result of lowered level of carbohydrate in the diet and thus substituting other caloric sources from carbohydrate would result in reducing triglycerides level.

Other studies, regarding beneficial effects of wheat bran indicated that some of the components (characterized as phenolic acids) associated with the fiber (rather than the whole fiber) could be involved in this context. Phenolic acids of wheat bran are composed of ferulic, vanillic and p-coumaric, caffeic and chlorogenic acids (Bryngelsson *et al.*, 2002). The health effects of these acids have mainly attributed to its antioxidant activities (Yilmaz and Toledo, 2004). A study of seven wheat varieties showed that ferulic acid is the predominant component accounting for about 46-67 % of total phenolic acids, and may contribute to the main antioxidant capacity of wheat (Zhou *et al.*, 2004). Phenolic antioxidants are reported to quench oxygen derived free radicals by denoting a hydrogen atom and, therefore, limit the risk of various diseases associated to oxidative stress such as diabetes (Fardet *et al.*, 2008). Interestingly, oat like wheat contains large amount of antioxidants, which are also concentrated within the outer layer of grain, they are mainly vitamin E, phytic acid and phenolic acids (Peterson *et al.*, 2002). The total phenolic acids, mainly (avenanthramides, vanillic and B-hydroxybenzoic acids) was significantly correlated with the antioxidant capacity of oats. Avenanthramides are typically found in oats and have antioxidant activity in vitro (Peterson *et al.*, 2002) and in vivo (Chen *et al.*, 2007). Avenanthramide is a more powerful antioxidant than some of the typical cereal components, such as ferulic, p-hydroxybenzoic, vanillic and phytic acids (Martinez-Tome *et al.*, 2004). To date, no comparative studies are available on the antioxidant capacity of oat bran and other plant products, such as wheat bran. However, in the present study, oat bran was more effective in reducing oxidative stress markers (MDA and PC) and increasing the antioxidant GSH in the diabetic rats than was observed by wheat bran, thus indicating a higher antioxidant capacity of oat bran. A finding that may be related to the presence of more avenanthramides in

oat bran, while wheat bran has high concentrations of many other phenolic components with less antioxidant activity (Martinez-Tome *et al.*, 2004). Accordingly, it can suggest that both oat bran and wheat bran have additional physiological effects as related to the role played by the antioxidant components associated with the two bran types, however oat bran attained higher antioxidant activity than wheat bran.

5. Conclusion:

Considering the above all findings, it can conclude that consumption of diets high in plant fibers, particularly soluble type appears to be effective in reducing onset of diabetes and associated heart disease, through favorably influencing a number of risk factors including serum glucose, lipids and oxidative stress markers. Thus, emphasis on consuming food rich in soluble fibers as oats might be a safe, effective and low cost approach for diabetic people at risk of developing heart disease.

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3/28/2011