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Interactions Between Total Plasma Homocysteine, Oxidized LDL Levels, Thiolactonase Activities and Dietary Habits in Tunisian Diabetic Patients

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1. Introduction

Cardiovascular disease (CVD) is the predominant cause for morbidity and mortality in diabetes mellitus (DM). Patients with diabetes mellitus have two to three times the incidence of atherosclerotic disease compared to the general population (Kannel & McGee, 1979). Several etiologic factors increase susceptibility to CVD in DM including insulin resistance, dyslipidemia, endothelial dysfunction, prothrombosis, and increased protein glycation (Baynes & Thorpe, 1999).

Plasma homocysteine levels are elevated in patients with diabetes, particularly in patients with type 2 diabetes as well as in individuals in prediabetic states who exhibit insulin resistance. Homocysteine (Hcy) is a non-essential amino acid that is produced from demethylation of methionine. Hcy can be remethylated into methionine by means of vitamin B12-dependent methionine synthase and 5-methyltetrahydrofolate as a methyl donor. Hcy can be also catabolized into cysteine (the transsulfuration pathway) via cystathionine beta synthase and cystathioninase, both enzymes being vitamin B6-dependent. A third way to remove Hcy is conversion to S-adenosylhomocysteine (SAH). The last reaction is mediated by SAH-hydrolase and favors the SAH formation in case of increased Hcy concentrations. S-Adenosyl methionine (SAM) is a universal methyl donor that is formed from methionine and converted into SAH after donating its methyl group. SAH is a potent inhibitor of most known methyltransferases (Kloor & Osswald, 2004).

Among the main determinants of tHcy levels in non-diabetic subjects are age, sex, renal function, several diseases, drugs, coffee and chronic alcohol consumption, smoking and physical inactivity (Refsum et al., 2006). Genetic factors and nutritional deficiencies of folate

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or of the vitamin cofactors (vitaminsB12, B6 and B2) involved in Hcy metabolism may also promote hyperhomocysteinemia. Besides other genetic defects, a thermolabile variant of Methylene Tetrahydrofolate Reductase (MTHFR), a key enzyme of the remethylation pathway, has been described (Frosst et al., 1995). It has been shown that this gene variation was associated with increased levels of homocysteine; Heterozygotes carrying MTHFR thermolabile variant have a reduced enzyme activity (down to 65% of normal levels), while homozygotes have only 30% of normal activity (Frosst et al., 1995). In type 2 diabetic patients, levels of homocysteine are influenced by their insulin concentrations, therapy with insulin, and medications such as metformin and glitazones that can either raise or lower homocysteine levels.

Epidemiological studies have identified elevated homocysteine (hyperhomocysteinaemia) as an independent risk factor for cardiovascular disease. Elevated levels of homocysteine (Hcy) above 12.1µmol/L have been shown to double the risk of pathophysiological conditions such as atherosclerosis, myocardial infarction, cerebral or peripheral vascular diseases (Castro et al., 2006). Mean plasma total Hcy (tHcy) was found to be significantly higher both in male and female patients with CAD compared to controls with angiographically normal coronary arteries (Kang et al., 1992). An increase in plasma Hcy of only 12% greater than the upper limit of normal was shown to be associated with an increase by 3.4- fold in the risk of myocardial infarction (Stampfer et al., 1992). After adjusting for possible confounders, Arnsen et al. (Arnsen et al., 1995) found a relative risk for coronary heart disease of 1.32 for an increase in serum Hcy of 4 μmol/l. A meta-analysis of 27 studies relating Hcy to coronary, cerebro vascular and peripheral arterial vascular diseases showed a very strong relationship between these diseases and tHcy (Boushey et al., 1995).

Elevated Hcy may also contribute to progressive atherosclerosis by several mechanisms, including arterial endothelial function impairment, oxidative stress induction, and the promotion of inflammation and thrombosis (Castro et al., 2006; Wald et al., 2002; 2004; Jakubowski, 2006). A unifying hypothesis for the mechanism of Hcy-mediated vascular injury has not yet been established. One frequently described mechanism involves oxidative damage, as Hcy can undergo autoxidation in the plasma or intracellularly, to form various reactive oxygen species (Welch & Loscalzo, 1998). The potent reactive superoxide and hydrogen peroxides, which are produced during this process, are mainly responsible for the vascular toxicity of homocysteine via the formation of oxidized low density lipoprotein (ox-LDL). The oxidation of LDL in the artery wall is believed to be the primary event leading to the initiation and progression of atherosclerosis (Steinberg & Witztum, 2002; Parthasarathy et al., 1998). Hcy has also been shown to decrease the activity (Nishio & Watanabe, 1997) as well as the expression of the antioxidant enzyme glutathione peroxidase (Upchurch et al., 1997). Creation of a prothrombotic environment by the action of Hcy on various factors involved in coagulation has also been proposed (Ratnoff, 1968; Fryer et al., 1993; Nishinaga et al., 1993). The reaction of Hcy with nitric oxide (NO) acts to prevent oxidative damage caused by Hcy but at the same time reduces the bioavailability of NO by trapping it intracellularly as a nitrosothiol (Jacobsen, 2001). Hcy is also a potent mitogen for vascular smooth-muscle cells (Harker et al., 1983; Tsai et al., 1994). Aggregates formed by the combination of Hcy thiolactone, a cyclical product of Hcy, with LDL (low-density lipoprotein) were shown to be taken up by intimal macrophages and be incorporated into atheromatous plaques (Naruszewicz et al., 1994). Hcy thiolactone is also incorporated into cellular and secretory proteins through lysine homocysteinylation, leading to the dysfunction of the proteins (Jakubowski, 1997). The high density lipoprotein (HDL) particle(s) is known to prevent the

formation of ox-LDL by means of the HDL-associated enzyme paraoxonase (PON); its antioxidant properties prevent the accumulation of lipid peroxides on LDL (Shih et al., 1998). Paraoxonase is a multifunctional antioxidant enzyme that not only can destroy Ox-LDL but also can detoxify the homocysteine metabolite, homocysteine thiolactone (Jakubowski H, 1997). In fact, human paraoxonase possesses a thiolactonase (HTase) activity, hydrolyzing Hcy thiolactone to Hcy (Jakubowski, 1999). Hcy thiolactone is likely a natural substrate of HTase/paraoxonase (Jakubowski, 2004) a product of the PON1 gene (Furlong et al., 1988).
The effect of diet on human health has already been underlined in many studies. During the past years population-based surveys and large-scale clinical trials have provided scientific evidence that diets, and especially those rich in fruits, vegetables, legumes, whole grains, fish and low-fat dairy products, are associated with lower incidence of various chronic diseases, including diabetes, cardiovascular disease and cancer (Ascherio et al., 1992; appel et al., 1997; Price & Fowkes, 1997; koubaa et al., 2007). Diet has also an important role among the factors affecting homocysteine levels. Mediterranean diet, with a high proportion of bioactive compounds (vitamins, polyphenols and flavonoids) proved its efficiency in lowering plasma homocysteine levels and reducing the incidence of cardiovascular disease.
The aim of the current study was to investigate whether elevated Hcy levels are associated with oxidation of LDL, and thiolactonase activity in type 2 diabetic patients, and further explore the contribution of various dietary components to prevent diabetes vascular complications and atherosclerosis progression.

2. Patients and methods

2.1 Study population

110 diabetic patients (54.2 ± 10.7 years) and 120 non diabetic healthy controls (44 ± 12.3 years) with available metabolic and life style informations were involved in this study. These patients did not receive any antioxidant drugs and none used hormonal replacement therapy. The following data were obtained: age, sex, weight. Height hip and waist circumference were measured using a standard scale. The study was approved by our hospital ethical committee, and informed consent was obtained from all patients before their enrolment. Major requirements for enrolment in all the groups were: absence of infectious or acute/chronic inflammatory diseases, known malignancy, absence of acute/chronic renal failure, or hepatic failure.

2.2 laboratory procedures

Validated laboratory procedures were used as described previously (Koubaa et al., 2008). Plasmatic total homocysteine (free and protein bound) was determined by a validated highly sensitive and accurate capillary gas chromatography mass spectrometry method (GC-MS) using a stable isotope as internal standard. Thiolactonase (HTLase) activity was estimated by a commercially available kit assay (Alfresa Auto HTLase; Alfresa Pharma Corporation, Japan). This method utilizes gamma-thiobutyrolactone as substrate and Ellman's procedure to monitor the accumulation of free sulfhydryl groups via coupling with 5,5-dithiobis(2-nitrobenzoicacid). Lipids and lipoproteins (Triglycerides: TG; total cholesterol: TC mmol/l, High density lipoproteins- cholesterol HDL mmol/l, Low density lipoproteins cholesterol: LDL mmol/l, triglycerides: TG mmol/l) concentrations were determined by enzymatic way. Apolipoproteins Apo A1 and Apo B were determined by an immunoturbidimetric method (Randox, Antrim, UK). Oxidized LDL levels (ox-LDL) were

measured by a sandwich ELISA method using a commercial kit (ox-LDL ELISA Kit; immunodiagnostic Bensheim,Germany). The dietary habits of the diabetic patients were evaluated. Food intakes were estimated by two dieticians using one-week diet recalls. Subjects were asked about their daily diet over a week period: they were asked about amounts, frequencies and variations in consumption. Nutrient intakes were calculated using the software Nutritionist IV computer analysis (Nutritionist IV Computer Analysis Program, 1994, Version 3.1, N2 Computing, Hearst Corp. Salem, OR).

2.3 Statistical analysis

Statistical analyses were assessed using the Statistical Package for Social Sciences (SPSS Inc., Chicago). Data are presented as median (25th to 75th interquartile range I.R) for several variables that were not normally distributed and comparison between the 2 groups was performed with the Mann–Whitney *U* test. The normally distributed values were expressed as means with standard deviations and group differences analyzed using the Student's t test. To test the association between the variables, either Pearson's correlations or Spearman's correlation rank (R) were used. Values of $p<0.05$ were considered to be statistically significant.

3. Results

3.1 Participants characteristics

The clinical and biochemical features of the healthy and diabetic patients are listed in table 1. Diabetic patients exhibited significantly higher mean values of systolic and diastolic blood

	Healthy controls (n=120)	Diabetics (n=110)	p
Age (years)	44 ± 12.3	54.2 ± 10.7	0.00
BMI (kg/m²)	26.7 ± 4.0	28.9 ± 5.7	0.00
WHR	0.91 ± 0.08	0.96 ± 0.07	0.01
SBP (mm Hg)	12.1 ± 1.2	14.6 ± 9	0.033
DBP (mm Hg)	7.06 ± 0.9	7.8 ± 1.2	0.00
Glucose (mmol/L)	5.23 ± 1	10.98 ± 4.2	0.00
Creatinine (µmol/L)	88.2 ± 19.3	85.8 ± 39.2	0.58
Urea (mmol/L)	4.9 ± 1.6	6.8 ± 2.7	0.00
Cholesterol (mmol/L)	4.4 ± 1.2	4.9 ± 1.4	0.00
Triglycerides (mmol/L)	1.3 ± 0.8	2.1 ± 1.2	0.00
HDL-C (mmol/L)	1.01 ± 0.28	1.01 ± 0.28	0.97
LDL-C (mmol/L)	2.7 ± 1.1	3 ± 1.5	0.08
ApoA1 (g/L)	1.29 ± 0.27	1.39 ± 0.43	0.1
ApoB (g/L)	0.83 ± 0.28	1.39 ± 0.43	0.03
tHcy (µmol/L) [£]	11.76 (10.7 – 12.81)	12.87 (9.7 – 17.5)	0.01
ox-LDL (ng/mL)	78.4 ± 23.7	139.6 ± 52.2	0.00
HTase (U/L)	569.9 ± 254	442.8 ± 211.8	0.01

SBP, DBP: systolic and diastolic blood pressure
Values are expressed as mean ± SD
*: $p<0.05$; **: $p<0.001$
[£]: expressed as median (I.R) and tested with the Mann Whitney's U test

Table 1. Clinical and biochemical features of the healthy Tunisians and diabetic patients

pressure (SBP and DBP), Waist to hip Ratio (WHR) and body mass index (BMI). As far as the biochemical features of the patients and healthy groups were examined, the diabetics exhibited significantly elevated urea levels as compared to healthy subjects (4.9 ± 1.6 vs. 6.8 ± 2.7, p= 0.00). Serum triglycerides and total cholesterol levels were also significantly higher in these patients (p = 0.00 and p=0.003 respectively) associated to significantly higher Apo B levels. In addition we found a significant increase in plasma homocysteine levels (11.76 (10.7 – 12.81) vs. 12.87 (9.7 – 17.5) µmol/l; P=0.01) associated with lower Thiolactonase activities (442.8 ± 211.8 vs. 569.9 ± 254 U/ml, P=0.01) and higher oxidized LDL levels (139.6 ± 52.2 vs. 78.4 ± 23.7 ng/ml p = 0.00) as compared to healthy subjects (table 1).

3.2 Correlations analysis

The correlations between plasma homocysteine levels, thiolactonase activities and oxidized LDL levels were then evaluated with some clinical and biochemical features in the diabetic patient's group. As expected, thiolactonase activities were associated negatively with tHcy levels (r= -0.554, p= 0.00), total cholesterol (r= -0.345, p< 0.05), LDL levels (r= -0.358, p< 0.05). Oxidized LDL levels were in opposite positively correlated with total cholesterol (r= 0.313, p< 0.05), creatinine levels (r= 0.353, p< 0.05) and BMI (r= 0.315, p< 0.05).

	tHcy	HTase	ox-LDL	BMI	TC	LDL-C	creatinine
tHcy	1.00	**-.554****	-.060	.080	.068	.036	.039
HTase	**-.554****	1.000	-.198	-.115	**-.345***	**-.358***	-.013
ox-LDL	-.060	-.198	1.00	**.315 ***	**.313***	.260	**.353***

*: p<0.05; **: p<0.001
£: tested with the Spearman's test of correlation

Table 2. Correlations between thiolactonase activity, plasma total homocysteine and oxidized LDL levels, with some clinical and biochemical features in the diabetic patients

3.3 Dietary surveys

As far as the dietary habits were considered we established that in the diabetic patients, the relative percentages of protein intakes per total calories were higher (12.4 ± 1.9 vs. 13.7 ± 3.8 %, p< 0.05) but the relative percentages of carbohydrate intakes per total calories were lower (50.7 ± 7.7 vs. 56.8 ± 5.4 %, p<0.001). The diabetic patient's diet was significantly richer in fats (30.8 ± 5.9 vs. 35.9 ± 7.5 %, p<0.00). They were consuming higher polyunsaturated fatty acids (14.2 ± 10.4 vs. 21.6 ± 17.4 %, p<0.00) but significantly lower monounsaturated and saturated fatty acids.

Finally, as the correlations with the nutrients and were examined we noticed that tHcy was positively correlated with intakes of protein (r = 0.267, p<0.00), saturated fatty acids (r = 0.334, p<0.00) and cholesterol (r = 0.265, p<0.05) as illustrated in table 4. Plasma homocysteine levels were also correlated with dietary sodium and zinc intakes. Thiolactonase activity was negatively associated with proteins (r = -0.345, p<0.05) and cholesterol intakes (r = -0.313, p<0.05). Ox LDL levels were positively correlated with lipid intakes in the diabetic patients (r = 0.324, p<0.05).

	Healthy subjects	Diabetics
Proteins (%)	12.4 ± 1.9	13.7 ± 3.8*
A/V	1.06 ± 0.27	1.1 ± 0.48
Carbohydrates (%)	56.8 ± 5.4	50.7 ± 7.7**
Fats (%)	30.8 ± 5.9	35.9 ± 7.5 **
SFA	23.2 ± 9.4	16.8 ± 8.1**
MUFA	46.9 ± 9.4	32.9 ± 14.8**
PUFA	14.2 ± 10.4	21.6 ± 17.4*
Cholesterol (mg)	188.2 ± 154	507.4 ± 206
Calcium(mg)	483.1 ± 154.3	507.4 ± 206
Vitamin B1 (mg)	0.49 ± 0.12	0.48 ± 0.16
Fiber (g)	16.3 ± 4.7	34.2 ± 15.5
Vitamin C (mg)	77.5± 30.4	82.7 ± 50.5
Vitamin E (mg)	7.1 ± 3.4	9.9 ± 10
Folates (µg)	134.4 ± 54.9	157.4 ± 71.2

A/V: percentage of Animal protein/ percentage of vegetal protein;
SFA: Saturated fatty acids,
MUFA: Monounsaturated fatty acids,
PUFA: Polyunsaturated fatty acids and.
*: p<0.05; **: p<0.001

Table 3. Daily nutrient intakes of the healthy and diabetic patients

	Proteins (%)	Fats (%)	SFA	Cholesterol	Sodium	Zinc
tHcy £	**.267****	-.138	**.334****	**.265***	**.324***	**.272***
HTase	**-.345***	.226	-.012	**-.313***	-.261	.211
ox-LDL	-.091	**.324***	-.028	-.038	-.234	-.260

*: p<0.05; **: p<0.001
£: tested with the Spearman's test of correlation

Table 4. Correlations between thiolactonase activity, plasma total homocysteine and oxidized LDL levels with selected nutrients in the diabetic patients

4. Discussion

Diabetic subjects constitute a patient population at high risk for cardiovascular disease, due to the influence of a clustering of risk factors. Plasma tHcy is considered as an emerging independent nontraditional risk factor for atherosclerotic vascular disease, which may enhance the effect of the traditional risk factors (Graham, 1997; Hackam & Anand, 2003). It is also a strong predictor of cardiovascular and all-cause mortality (Bostom et al., 1999). Therefore, it is important to know if dietary habits and lifestyle can affect plasma tHcy levels in this population, and eventually select the patients who would be at a higher risk for developing such complications. In the present study, tHcy levels

were higher in the diabetic patient's group. Plasma tHcy levels have been studied extensively in diabetic, as well as in non-diabetic subjects. A number of studies did not find any differences in plasma tHcy values between diabetic and control subjects (Salarde et al., 2000; Lanfredini et al., 1998; Pavia et al. 2000, Diakoumopoulou et al., 2005). Some investigators demonstrated lower levels of tHcy in diabetics versus controls (Matteucci et al., 2002; Wollesen et al., 1999; Salardi et al., 2000). However, our findings are in accordance with other reports where tHcy were higher in the diabetic patients (Passaro et al., 2000; Yeromenko et al., 2000). Furthermore, homocysteine increases the production of ox-LDL and enhances their uptake by macrophages leading to the formation of foam cells that play a crucial role in atherosclerotic lesions (Tsai et al.,). Ox-LDL are considered as biochemical markers of coronary artery disease (Toshima et al., 2000 ; Holvoet et al, 2001). Accordingly, we found high levels of ox-LDL in diabetic patients exhibiting the highest levels of tHcy, which confirms the oxidative effect of homocysteine in the type 2 DM patients. Every 5 µM/L increase in the Hcy concentration increases the risk of CVD by 50%, and TC levels by 20 mg/dL. (Castro et al., 2006; Wald et al., 2002; Nygard et al., 1998; Genset et al., 1990). The mechanisms possibly responsible for causing endothelial dysfunction include changes in LDL, and Ox- LDL. The oxidation of LDL is increased by the combination of thiolactone and apo B's free lysyl epsilon amino residue (Rocchi et al., 2007; Mansoor et al., 1993, 2000). When LDL is reacted with Hcythiolactone in methionine, which is an explicit initiator of arteriosclerosis, LDL-binding thiol is increased by 250 nM per mg of LDL protein (Ferguson et al. 1999). The free amino- or thiol-adducted LDL causes aggregation, and increases LDL uptake in macrophages and atheroma production by lipids (Perna et al., 2003). Another mechanism by which Hcy may cause LDL oxidation is a possible deformation of LDL through Hcy autoxidation, which causes the oxidation of side chains of LDL such as fatty acids or apo B- 100 (Young & Woodside , 2000). Both Hcy and Ox-LDL could participate in thrombosis by increasing VCAM-1 and ICAM-1, caused by endothelial cell activation due to fibrinogen-platelet GPIIb-lIIa formation. Ox-LDL affects both initial and progressive stages of arteriosclerosis (Jakubowski, 2000; Dardik et al., 2000; Vadachkoria et al., 2004; Erl et al., 2000). On the other hand, circulating Hcy reduces NO-induced detoxification, vasodilation, and endothelial function (Rocchi et al., 2007). NO participates in a metabolic pathway (S-nitroso-HCY) that is able to protect against Hcy-induced endothelial oxidative damage. Paraoxonase plays also a key role in reducing Hcy endothelial damages. In our previous results, we found a decline in endogenous antioxidant defense system capability in type 2 DM patients indicating their high oxidative stress (Smaoui et al., 2006). Antioxidant status of enzymes in DM patients is controversial. Several authors have reported that lipid peroxides level increases in type 2 DM patients (Mooradian, 1991); on the other hand, other studies found no significant increase in these patients (Velazquez et al., 1991). Among the numerous antioxidant enzymes, we focused in the present study on the thiolactonase activities which were decreased in the diabetic patients. Most studies evaluated the paraoxonase activity in Type I and Type II diabetic patients and found a decreased activity in these patients (Boemi et al., 2001; Kordonouri et al., 2001; Letellier et al., 2002; Mackness B et al., 1998; 2002; Agachan et al., 2004). Paraoxonase is a multifunctional antioxidant enzyme that not only can detoxify paraoxon, destroy oxidized low-density lipoprotein (ox-LDL) but also can hydrolyze homocysteine thiolactone.

The mechanism by which PON1 is reduced in diabetes is poorly understood, but may be associated with an increase in blood glucose concentration. Glycation can both inactivate PON1 and increase lipid peroxidation in HDL (Hedrick et al., 2000). Glycated HDL also has a reduced ability to protect against oxidation (Ferretti et al., 2001). PON1 activity and concentration were decreased also in studies of healthy subjects with elevated fasting glucose levels (Leviev et al., 2001; Kordonouri et al., 2001). Our finding showed a negative association between HTase activities, tHcy levels and oxidized LDL levels. These levels were associated with higher triglycerides, total cholesterol and also higher Apo B levels. Apo B is superior to cholesterol and triglycerides as a coronary syndrome risk factor due to the heterogeneity of lipoprotein particle composition. In fact, plasma Apo B concentrations reflect the number of atherogenic lipoprotein particles including LDL, and chylomicron remnants which contain variable amounts of triglycerides and cholesterol, but each of these particles contain 1 molecule of Apo B as structural protein. Then, higher levels of Apo B found in the diabetic patients reflects their higher risk for developing cardiovascular diseases (Sniderman et al., 1997).

The SBP and DBP were also increased in the diabetic patients. The association between homocysteine and chronic complications of diabetes mellitus could be explained by different mechanisms; direct toxic effect on vascular endothelial and indirect effect on the normal methylation in endothelial cells (Weir & Molloy, 2000). Direct toxic effect of homocysteine could be mediated by damage to vascular endothelial cells, resulting in vascular events, such as microvascular disease. In the study of Fiorina et al. (Fiorina et al., 1998), Caucasian patients with elevated tHcy levels had significantly higher diastolic pressure and mean arterial pressure. These results are similar to our data. Other populations (Indians) have shown correlation between homocysteine concentrations and body weight (Das et al., 1999). Our results did not show correlations among tHcy and different anthropometric parameters (body mass index, waist to hip ratio). Nevertheless, a positive correlation between ox-LDL levels and BMI was established in the diabetic patients. There was also a positive association between ox-LDL levels and creatinine levels in the diabetic patients. No correlation was found between creatinine and tHcy levels. Most studies have been able to show a positive correlation between plasma Hcy and plasma creatinine levels, suggesting the importance of the kidney in the regulation of plasma Hcy. Renal function in Type 2 diabetes appears to change with the progress of the disease: hyperfiltration in the early stages and progressive deterioration with the progression of diabetes. Diabetes therefore provides an interesting situation with changes in kidney functions being superimposed on the already existing changes in the metabolic milieu. Moreover, we found a negative association between HTase activities tHcy levels and the levels of total cholesterol and ox-LDL. In fact, in certain diseases e.g. diabetes where HDL size is reduced, secretion of PON1 is affected due to the fact that PON1 tends to bind to larger sized species of HDL both *in vivo* (Blatter et al.,1993) and *in vitro* (Deakin et al., 2002). In addition, *in vitro* studies demonstrated that PON1 was inactivated by oxidized lipids and oxidized LDL (Aviram et al., 1999). PON1 is highly susceptible to inactivation by oxidation. In vitro, PON1 activity is protected by the antioxidant polyphenols quercetin and glabridin (Aviram et al., 1999), suggesting that dietary antioxidants may play a similar role in vivo. Studies have shown that consumption of pomegranate juice, rich in polyphenols and other antioxidants, can raise PON1 activity up to 20% in both humans and apoE knockout mice (Kaplan et al., 2001). Polyphenols extracted from red wine also increase PON1 activity in mice (Hayek et al.,

1997). Recent work from Gou´edard et al. (Gou´edard et al., 2004) provides evidence that dietary polyphenols can influence PON1 gene expression. Clinical trials of the antioxidant vitamins C and E have, to date, been unsuccessful in showing a link between vitamin intake and CHD risk. Likewise, their effect, if any, on PON1 activity is not clear. Jarvik et al. (Jarvik et al., 2002) found that PON1 activity correlated positively with the quantity of vitamins C and E in the diet; however, another study in which vitamin E was given to volunteers showed no change in PON1 activity (Arrol et al., 2000). In contrast, oleic acid from olive oil is associated with increased activity (Tomas et al., 2001; Wallace et al., 2001). Meals rich in used cooking fat, which contains a high content of oxidized lipids, were followed by a significant fall in PON1 activity when fed to healthy men (Sutherland et al., 1999). These correlations were not confirmed by our results. The thiolactonase activities were correlated negatively with protein and cholesterol intakes. Plasma homocysteine levels were in opposite positively correlated to protein intakes, the relative percentage of fats and saturated fatty acids in diet and sodium intakes. Accordingly, in the Hordaland study that included 5917 subjects, a higher intake of saturated fatty acids was positively associated with higher concentrations of plasma Hcy. Concentrations of Hcy were higher (by 8.8%) in the group with the highest intakes of saturated fatty acids compared to that with the lowest intake (Berstad et al., 2007). Food-based feeding trials have shown a reduction in blood Hcy in subjects who consume fortified cereals or whole grains in combination with fruits, vegetables and low fat dairy products (Lutsey et al., 2006; Appel et al., 2000). Several carefully studied populations in Mediterranean countries and in some areas in Asia, where traditional diets consist largely of foods of plant origin, exhibit low rates of many chronic diseases and long life expectancies. Many case-control and prospective studies have provided further evidence that high consumption of plant foods confers numerous health benefits. Although the mechanisms are not fully understood, carotenoids, folic acid, and fiber, all of which are abundant in the Mediterranean diet, appear to play important roles in the prevention of coronary artery disease (Kushi et al., 1995).

5. Conclusion

In conclusion, Hcy and thiolactonase activities and oxidized levels are interrelated in type 2 diabetic patients and are responsible, at least partly, of the vascular complications. Strong evidence suggested that excess of plasma homocysteine disturb lipid metabolism via the oxidation of LDL particle and its aggregation, and enhancing atherosclerosis progression. Another line of evidence suggested that thiolactonase activity is affect in diabetics partly by a glycation process that accentuates the endothelial damages of homocysteine. A very interesting aspect to be tested in future studies is the beneficial effect of certain nutriments on lipid parameters and plasma homocysteine levels. Future long-term studies on larger populations are needed for determining the exact role of homocysteine in the development of diabetes vascular complications and the metabolic ways of prevention.

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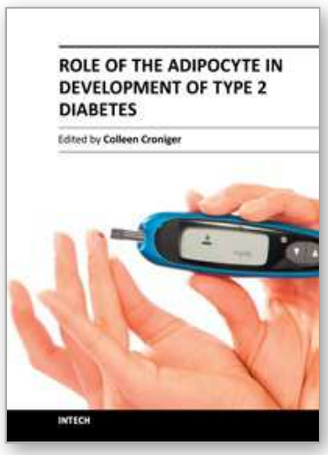

Role of the Adipocyte in Development of Type 2 Diabetes

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Adipocytes are important in the body for maintaining proper energy balance by storing excess energy as triglycerides. However, efforts of the last decade have identified several molecules that are secreted from adipocytes, such as leptin, which are involved in signaling between tissues and organs. These adipokines are important in overall regulation of energy metabolism and can regulate body composition as well as glucose homeostasis. Excess lipid storage in tissues other than adipose can result in development of diabetes and nonalcoholic fatty liver disease (NAFLD). In this book we review the role of adipocytes in development of insulin resistance, type 2 diabetes and NAFLD. Because type 2 diabetes has been suggested to be a disease of inflammation we included several chapters on the mechanism of inflammation modulating organ injury. Finally, we conclude with a review on exercise and nutrient regulation for the treatment of type 2 diabetes and its co-morbidities.

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