

Lipid Profile and Hepatic Enzymes Differences between Pre-diabetes and Normal Staff

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Abstract: Purpose: The aim of this study was to investigate lipid profile and hepatic enzymes difference between pre-diabetes and normal subjects. Methods: In this cross-sectional study, 264 employees of Energy Industries Engineering & Design (EIED) Company were randomly selected and participated in the study in January 2019. A sample of 10 mL of venous blood was obtained between 8 a.m. and 10 a.m. Blood analyses for fasting glucose (FG), total cholesterol (TC), triglyceride (TG), LDL-cholesterol, HDL-cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels were determined by enzymatic methods. Body composition and anthropometric indices were measured and recorded using the OMRON BF511 device and tape measure. Achievements of This Study: TG, the LDL/HDL ratio, and the ALT were significantly higher in the pre-diabetes group. Also, body mass index, waist circumference, waist-hip ratio were significantly higher in pre-diabetic women than in normoglycemic women. According to the results of this study suggested that the risk of cardiovascular and liver diseases in people with pre-diabetes increases and the intervention of lifestyle such as increased levels of physical activity and exercise to prevent diabetes and related complications.

Keywords: Diabetes, aged, liver disease, exercise, physical activity.

1. Introduction

The prevalence of a sedentary lifestyle in different societies is associated with the increase of various diseases such as cardiovascular disease, hepatic disease, cancer and early mortality [1, 2]. Reports suggest that 4% of the Tehran adult population is diagnosed with pre-diabetes every year [3] which causes to the development of type 2 diabetes prevalence and its related complications.

Meanwhile, people's job plays a fundamental role in their daily physical activity, in which it has been reported that office employees spend 66 to 82% of their time inactive and almost 75% in seated positions, which lead to increased risk of obesity and its related diseases, such as diabetes, non-alcoholic fatty liver disease, and cardiovascular disease [4-7]. Also,

Dunstan et al. [8] demonstrated that people with office jobs who spend most of their time seated and have a sedentary lifestyle, have higher blood glucose than the normal range people and also these individuals are more at type 2 diabetes risk.

It has been reported that with the continuation of sedentary lifestyles in different societies, the number of diabetic patients aged 20 to 79 will increase from 285 million in 2010 to 439 million in 2030 [9] and this will be associated with great concerns such as economic, social and health issues. On the other hand, the lack of control of type 2 diabetes can lead to many injuries, including heart disease, fatty liver disease, atherosclerosis, hypertension and stroke [10, 11]. Diabetic patients are two to four times more susceptible to develop cardiovascular disease than non-diabetics [12]. The term pre-diabetes is defined as the border between normal blood glucose and type 2 diabetes [13, 14]. According to the report of the American Diabetes Association (ADA) [15],

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pre-diabetic people are diagnosed with fasting blood sugar of 100 to 125 mg/dL. According to the Centers for Disease Control Prevention (CDC) [13], the prevalence of pre-diabetes is much higher than diabetes. Also, regarding the International Diabetes Federation (IDF), the prevalence of diabetes among the Iranian adult population (between 20 and 79 years old) in 2014 has been estimated at 8.6% (approximately 4.5 million) [16]. Moreover, in 2010, It was shown that the annual growth rate of diabetes in Iran is higher than the global average and will reach the second rank in the Middle East by 2030 [9].

Identifying and controlling the risk factors for type 2 diabetes can be essential for preventing diabetes and its related diseases. Sugden et al. [17], in 2011 reported that dyslipidemia leads to insulin resistance and type 2 diabetes by impairing the function of the enzymes involved in lipid metabolism. Several studies [18, 19] have reported that dysregulation in serum lipid levels (dyslipidemia) is independent of the reduction in insulin among diabetic patients. Furthermore, numerous reports have shown that serum levels of lipids indices are highly changing in diabetic patients, providing the context for cardiovascular disease and other metabolic diseases [18, 20].

On the other hand, increased activities of liver enzymes such as aspartate aminotransferase (AST) and alanine aminotransferase (ALT) are important markers of liver injury which is frequently associated with type 2 diabetes [21]. On the other side, alkaline phosphatase (ALP) is another hepatic enzyme that has been reported to be increased in type 2 diabetic patients [22]. In addition, it has been identified that elevated ALP levels are associated with disruption of inflammatory factors homeostasis such as tumor necrosis factor- α (TNF- α) and reactive protein C (CRP), which play important roles in insulin resistance and development of type 2 diabetes [22].

Changes in plasma glucose levels which usually associated with changes in lipid and hepatic profiles play a key role in the development of cardiovascular

diseases, liver diseases and premature deaths [18]. On the other hand, the majority of the existing studies have examined the above indices in diabetic patients compared to normal individuals. Therefore, the primary purpose of the present study was to investigate the lipid profile and hepatic enzymes difference between pre-diabetes and normal subjects.

2. Material and Method

2.1 Study Design and Subjects

This cross-sectional study was a part of annual health examinations conducted in Energy Industries Engineering & Design (EIED) Company in January 2019. The checkup included a medical history, validated health-related questionnaires, anthropometric measurements and standard laboratory tests. A total of 264 office employees aged 25-68 years randomly participated in our study. Our sample population dropped to 255 due to exclusion criteria. All participants gave their informed consent. Criteria for sampling selection were people who worked in EIED with at least 1-year work experience, and willing to participate. Subjects with missing data, pregnant women and those diagnosed with cardiovascular disease, diabetes, hypertension and liver diseases were excluded. According to American Diabetes Association (ADA) individuals were classified as normoglycemic ($n=120$, with fasting glucose level of 99 mg/dL or lower), and prediabetic ($n=135$, with fasting glucose level between 100 and 125 mg/dL). Also, the researchers ensured that participants' identity and what they said or did during the research were maintained confidential. In addition, they were given a detailed explanation about the study's purpose and methods. The research protocol was approved by the Health Committee of the Information Services Corporation (Iran).

2.2 Collection of Blood Sample

A sample of 10 mL of venous blood was obtained between 8 a.m. and 10 a.m. from each subject in a

seated position after overnight fasting (8-12 h). Samples were collected and centrifuged for 10min at 3,500rpm for plasma collection. Blood analyses for fasting glucose (FG), total cholesterol (TC), triglyceride (TG), LDL-cholesterol, HDL-cholesterol, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP) levels were determined by enzymatic methods. The serum lipid profile was categorized as follows: LDL<70mg/dL is optimal, 130-159mg/dL is borderline, >160mg/dL is high; HDL<50mg/dL is low (for women), <40mg/dL (for men), 50-59 is normal (for women),40-50mg/dL (for men), >60mg/dL is high (both women and men); Chol<200mg/dL is optimal, 200-239mg/dL is borderline, >249mg/dL is high; TG<150mg/dL is optimal, 150-159mg/dL is borderline, 200-499mg/dL is high. Normal ALT, AST and ALP for both sexes were defined as ALT of 7-56 U/L, AST of 8-48 U/L and ALP of 40-129 U/L respectively.

2.3 Measurements of Anthropometric, Body Composition and Blood Pressure

Weight, body fat percentage, muscle mass percentage and visceral fat were measured by body analysis device (OMRUN Bf511) with light clothing and bare feet. Height was measured to the nearest 0.1 cm using a wall-sticker tape meter. BMI was calculated using height and weight measurement

(kg/m²). Waist circumference (WC) was measured to the nearest 0.1 cm in standing position using plastic tape placed at the midpoint between the lower rib and the iliac crest. Hip circumference was measured at the greatest point of the buttocks. Then waist-hip ratio (WHR) was calculated by dividing waist and hip circumferences.

2.4 Statistical Analysis

Continuous variables were assessed for normality using a Kolmogorov-Smirnov test. Variables were presented as mean \pm S.D., frequencies and percentages. The difference between groups was tested using an independent-sample *t*-test. A *p*-value <0.05 was considered as a level of significance. All analysis was performed with SPSS version 21.

3. Result

Out of 255 individuals enrolled in our study 135(53%) were having impaired fasting blood glucose. The characteristics of prediabetic and normoglycemic subjects by gender are summarized in Table 1.

The comparison between the groups highlighted that BMI, WC and WHR were significantly different among female subjects. Table 2 shows the distribution of lipid profile and hepatic enzymes between normoglycemic and prediabetic groups.

Table 1 Characteristics of subjects according to fasting blood glucose and gender.

Variables	Males			Females		
	Mean \pm S.D.		<i>P</i> value	Mean \pm S.D.		<i>P</i> value
	Prediabetic (n=104)	Normoglycemic (n=66)		Prediabetic (n=31)	Normoglycemic (n=54)	
Age(yrs)	41.8 \pm 8.19	39.4 \pm 6.61	<0.05	40.5 \pm 6.06	39.3 \pm 5.16	0.335
Education(yrs)	16.2 \pm 2.85	15.8 \pm 3.14	0.495	16.5 \pm 1.73	16.9 \pm 1.92	0.380
Weight(kg)	81.5 \pm 11.01	81.1 \pm 10.80	0.824	67.4 \pm 9.24	64.4 \pm 8.35	0.131
Height(cm)	174.7 \pm 6.65	175.7 \pm 6.58	0.326	161.2 \pm 6.42	161.9 \pm 5.80	0.599
BMI (kg/m ²)	26.8 \pm 3.42	26.3 \pm 3.59	0.314	25.8 \pm 2.95	24.4 \pm 2.77	<0.05
Body fat (%)	26.5 \pm 5.49	25.7 \pm 5.66	0.335	38.0 \pm 5.64	37.4 \pm 4.81	0.619
Muscle mass (%)	34.3 \pm 2.98	34.9 \pm 2.98	0.208	26.0 \pm 3.15	25.3 \pm 2.11	0.292
WC (cm)	87.3 \pm 9.04	86.6 \pm 10.23	0.643	79.7 \pm 8.08	74.4 \pm 6.53	<0.01
HC (cm)	99.9 \pm 6.29	99.4 \pm 5.95	0.604	100.1 \pm 6.51	99.7 \pm 6.59	0.803
WHR	0.87 \pm 0.05	0.86 \pm 0.06	0.732	0.79 \pm 0.07	0.74 \pm 0.05	<0.01

WC: waist circumference, HC: hip circumference, WHR: waist to hip ratio.

Table 2 Lipid profile and hepatic enzymes in normal and prediabetes groups.

	Gender	Levels	Normal	Pre-diabetes
TG	Both	Desirable	87 (72.5%)	71 (52.59%)
		Borderline	16 (13.33%)	25 (18.52%)
		High	17 (14.17%)	39 (28.89%)
Cholesterol	Both	Desirable	75 (62.5%)	79 (58.52%)
		Borderline	34 (28.33%)	40 (29.63%)
		High	11 (9.17%)	16 (11.86%)
HDL	Men	Desirable	12 (18.18%)	16 (15.24%)
		Borderline	27 (40.91%)	39 (37.14%)
		High	27 (40.91%)	50 (47.62%)
	Women	Desirable	20 (37.04%)	7 (24.14%)
		Borderline	19 (35.19%)	6 (20.69%)
		High	15 (27.78%)	16 (55.17%)
LDL	Both	Desirable	106 (88.33%)	115 (85.19%)
		Borderline	8 (6.67%)	17 (12.59%)
		High	6 (5%)	3 (2.22%)
LDL/HDL	Both	Desirable	79 (65.84%)	64 (47.41%)
		Borderline	28 (23.33%)	43 (31.86%)
		High	13 (10.83%)	28 (20.74%)
ALP	Both	Low	4 (3.33%)	3 (2.22%)
		Normal	116 (96.67%)	131 (97.04%)
		High	0	1 (0.74%)
AST	Both	Low	0	1 (0.74%)
		Normal	119 (99.17%)	132 (97.78%)
		High	1 (0.83%)	2 (1.48%)
ALT	Both	Low	1 (0.83%)	0
		Normal	114 (95%)	123 (91.11%)
		High	5 (4.17%)	12 (8.89%)

Table 3 Comparison of health profile in prediabetic and normoglycemic subjects.

Variables	Prediabetic (N=135)	Normoglycemic (N=120)	P
Chol (mg/dL)	193.41 ±36.08	193.38 ±33.56	0.994
TG (mg/dL)	168.67 ±92.51	133.87 ±76.63	0.001**
HDL (mg/dL)	43.61 ±11.33	49.35 ±12.19	0.000**
LDL (mg/dL)	103.84 ±25.58	102.21 ±29.15	0.634
LDL/HDL ratio	2.54 ±0.84	2.22 ±0.90	0.003**
ALP (U/L)	69.33 ±18.47	65.57 ±15.94	0.085
AST (U/L)	23.32 ±8.79	22.11 ±6.80	0.224
ALT (U/L)	32.68 ±21.30	27.12 ±15.47	0.019*

Chol: cholesterol, TG: triglyceride, HDL: high-density lipoprotein, LDL: low density lipoprotein, ALP: alkaline phosphatase, AST: aspartate aminotransferase, ALT: alanine aminotransferase.

* Correlation is significant at the 0.05 level (2-tailed).

** Correlation is significant at the 0.01 level (2-tailed).

As presented in Table 3, the prediabetic group, versus the normoglycemic group, showed significantly higher triglyceride, LDL/HDL ratio and

lower HDL cholesterol ($p < 0.01$). Neither cholesterol nor LDL showed a significant difference in this regard. Also, there was no significant difference in AST and

ALP between normal glucose and prediabetic subjects. However, ALT was significantly higher in the prediabetic group ($p < 0.05$).

4. Discussion

Changes in lipid profile and liver enzymes can lead to the development and exacerbation of cardiovascular, hepatic, metabolic, hypertensive and stroke diseases by affecting different organs of the body. Many factors, such as the use of medication and genetic factors, lead to changes in fat metabolism in individuals with diabetes. On the other hand, changes in hepatic enzymes have been reported in diabetic patients, which are associated with liver diseases, including non-alcoholic fatty liver disease. Early identification and control of type 2 diabetes-related indices can be an effective strategy to prevent, control and treat type 2 diabetes and its related complications.

In the present study, triglyceride levels were significantly higher in pre-diabetic subjects than in normal subjects ($p < 0.001$). Our results in this regard were consistent with the findings of Ozder in 2014 [23] and Kansal and Kamblein 2016 [24]. In pre-diabetic patients, the body's resistance to glucose increasing, leads to increased production of triglyceride in the liver and intestine, as a result, increases cell access to free fatty acids [18, 24]. This insulin resistance also reduces the inhibition of hormone-sensitive lipase in adipose tissue, leading to increased lipolysis, FFA flux to the liver and TG production by the liver [18]. In addition, an increase in blood glucose and impaired glucose tolerance results in decreased insulin sensitivity and insulin secretion deficiency. These conditions also lead to increased secretion of TG from the liver to supply free fatty acids as fuel for cells, which ultimately is associated with hypertriglyceridemia in these individuals [25].

In the present study, HDL in pre-diabetic patients was significantly lower than in normal subjects ($p < 0.001$). Our findings were in line with the results

of Gatti et al. in 2009 [26] and Waldman et al. in 2014 [27]. With an increase in blood glucose and body cell resistance to insulin, the activity of hepatic lipase increases (HDL catabolism-controlling enzyme), resulting in the conversion of large HDL particles to smaller particles, faster HDL clearance of bloodstream and a significant decrease in HDL [25].

In the present study, there was no significant difference in plasma LDL levels between pre-diabetic and normal subjects. Our findings were in agreement with the findings of Wang et al. in 2012 [28] and Stolinski et al. in 2008 [29]. In diabetic subjects, LDL catabolism is reduced, leading to the prolonged LDL levels in serum and lipid deposition in the artery wall [29]. On the other hand, hepatocyte LDL receptor plays an important role in the LDL catabolism, and elevated blood glucose and increased insulin resistance leading to decreased sensitivity of LDL receptor in the liver, its low expression and consequently to decrease LDL catabolism and raise its levels in the blood [25]. Also, the study of Duvillard et al. in 2003 [30] reported that type 2 diabetes mellitus is the most important factor in the reduction of LDL receptors expression and its increase in serum levels. On the other hand, a study by Kansal and Kamblein 2016 [24] showed that serum LDL levels in pre-diabetic individuals were significantly higher than in healthy individuals. The reason for the discrepancy between our findings may be due to the lack of control and consideration of the initiating time of subjects' disease.

In the present study, there was no significant difference between serum total cholesterol in pre-diabetic and normal subjects. Most research in this area has reported that pre-diabetes status is generally associated with hypertriglyceridemia and HDL reduction and also has no significant effect on serum total cholesterol levels [31-33]. However, the total cholesterol of patients with type 2 diabetes is significantly higher in healthy and pre-diabetic individuals [33].

In the present study, LDL/HDL ratio in pre-diabetic subjects was significantly higher than healthy subjects ($p < 0.003$). Our findings were in contrast with the study of Kansal and Kamblein 2016 [24] and Miyazaki et al. in 2012 [34]. Regarding the lack of significant differences between LDL levels of pre-diabetic and normal subjects in our study, the reason for the increase in LDL/HDL ratio can be attributed to changes in the levels of hepatic lipase enzyme and subsequently a significant decrease in HDL levels in pre-diabetic subjects.

The liver as a site of glycogen synthesis, gluconeogenesis and insulin degradation, plays an important role in plasma glucose homeostasis [35]. Therefore, changes in hepatic enzymes can be considered as an indicator of liver dysfunction in pre-diabetic patients. In the present study, serum levels of ALT in pre-diabetic subjects were significantly higher than healthy subjects. Our finding is consistent with those of other studies conducted by Nguyen et al. in 2011 [36] and Cho et al. in 2007 [37]. ALT is an enzyme most commonly found in the liver and kidney cells and its concentration is typically low in blood, but liver damage causes the release of ALT into the blood and increases its serum levels [38]. The biological mechanisms that explain the contributed factors in liver enzymes increment among pre-diabetic patients have not been fully understood. However, one possible mechanism may be related to central obesity that occurs in pre-diabetic and diabetic individuals [39]. Central obesity has been shown to be associated with an increase in insulin resistance (commonly present in pre-diabetic and diabetic individuals) that results in impaired adipokine secretion as well as increased tumor necrosis factor (TNF α), interleukin 6 (IL-6), resistin and adiponectin reduction, and these factors may eventually lead to liver dysfunction in diabetic and pre-diabetic individuals following changes in liver enzyme levels [40].

In the present study, there was no significant difference between serum levels of AST and ALP in

pre-diabetic and normal subjects. Increased ALP and AST enzymes have been reported mostly in people with type 2 diabetes [22]. Studies have shown that ALP is a potent marker in the development of insulin resistance in diabetics [41]. Experimental studies have reported that ALP plays an important role in antioxidant defense in most types of cells through the stimulation of extracellular glutathione transport [22]. In other words, increased oxidative stress in type 2 diabetic patients leads to increased ALP activity which consequently increases its serum levels [22]. The lack of a significant increase in these enzymes in our subjects is probably due to the fact that they have not yet reached the type 2 diabetes stage, which is associated with a significant increase in oxidant levels in the body.

BMI and WHR of pre-diabetic women were significantly higher than normal women, but no significant difference was found in male subjects. In a study of the Iranian population, Haghghatdoost et al. in 2017 [42], reported that BMI and WHR could be used as predictors of type 2 diabetes and the effect of increased BMI and WHR on blood glucose elevation was higher in men. The positive effect of exercise on improving body composition and anthropometric indices has been documented in several studies.

Batacan et al. in 2016 [43] reported that high-intensity interval training is an appropriate strategy to modify anthropometric indices (waist circumference and WHR) and body composition (fat percentage, BMI, muscle mass) which are associated with reduced risk of metabolic and cardiovascular diseases. On the other hand, Tartibian et al. in 2019 [44] reported the positive effect of moderate-intensity aerobic exercise on fat percentage and weight loss in obese girls.

5. Conclusion

Lifestyle modifications through increased physical activity and improved diet can be used as appropriate strategies to reduce and control the blood glucose and

its related diseases such as cardiovascular and liver diseases in pre-diabetic people.

6. Limitation and Strength

One of the limitations of this study is the small statistical population. Sampling from office workers in a larger community such as Tehran or the whole country can provide more accurate information about the prevalence of pre-diabetes and its association with lipid profiles and liver enzymes. In addition, a review of the history of pre-diabetes in these individuals and their categorization based on the duration of pre-diabetes may be used as an excellent variable to predict pre-diabetes and other biochemical markers in future studies.

In this study, our subjects were adults with office position, and given the increased working hours and sitting time in developing countries, as well as the high risk of diabetes in these people and related diseases in older age, it can be stated that we have addressed one of the most important issues related to community health by examining the factors associated with pre-diabetes status.

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Disclosure Statement

No potential conflict of interest was reported by the authors.

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