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Chapter 4

Can Adiponectin be a biomarker for Ethnic heterogeneity in Diabetes Mellitus?

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Additional information is available at the end of the chapter

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1. Introduction

There is considerable body of evidence to suggest that the effect of obesity as a major risk factor of chronic diseases differ due to variation in genetic predisposition and ethnic differences. This is due probably to the difference in body habitus and the distribution of adipose tissue. It is shown that Asians have a higher proportion of abdominal obesity compared to other ethnic groups and carry greater risk for diabetes, hypertension and coronary vascular diseases at a lower level of body mass index(BMI) compared to other populations. [1-3]. Japanese are reported to carry twice the risk of developing diabetes at all levels of BMI compared to Caucasians [4]. Therefore with a wide variety of studies reporting the importance of ethnicity playing an important role in the distribution of total body fat has created a need to identify a biomarker(s) or risk marker for ethnic heterogeneity in the development of chronic diseases.

In this regard adipocytokines adiponectin, leptin and resistin are considered as potential candidates to delineate the mechanisms involved in such ethnic differences related to chronic diseases. Adiponectin and leptin are reported to show reciprocal relationship with increasing adiposity. It is demonstrated that adiponectin levels reflect visceral adiposity and leptin the subcutaneous one. It is also reported that serum adiponectin levels are lower in Chinese, Malay, Japanese, Koreans, south Asians compared to Caucasians. [5]There is another adipocytokine which is related to adiposity. This adipocytokine was reported to resist the action of insulin and so it is named as Resistin. It is shown that Resistin is present more in visceral adipose tissue compared to other fat depots and a diet rich in fat induces greater secretion of resistin.[6] The adiponectin, leptin and resistin trio could be the biomarkers of ethnic heterogeneity.

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Obesity is a major public health concern of Libya with higher prevalence of obesity related diseases hypertension, type 2 diabetes (T2DM) and coronary vascular disease.[7] Therefore, the present preliminary study was undertaken in Libyan subjects with their unique ethnicity, life style and cultural habits to demonstrate whether such differences occur in serum adiponectin, leptin and resistin levels in relation to adiposity particularly visceral adiposity. It was shown that BMI and Waist circumference could be taken as markers of subcutaneous obesity and abdominal obesity respectively. Along with these anthropometric measurements glycemic status, lipid profile were studied and correlated with adiponectin, leptin and resistin levels in obese and type 2 diabetes (T2DM) subjects.

2. Subjects taken for the study

The subjects included in the study were local Libyan subjects, Benghazi. Informed consent was taken from each participant and approval for the study taken from Institute Ethics Review Board(Faculty of Medicine, Benghazi University, Benghazi).

3. Anthropometric measurements

Height, weight, waist circumference, were measured. Their age, duration of diabetes and medicine usage as well as personal and family history were noted.The measurements and examinations were carried out by the same physician.

BMI was calculated by the formula: Weight (kg)/Height2 (m2). Normal BMI was taken as 18-25 kg/m2. Patients with BMI values of 25-30 kg/m2 were classified as overweight; and those with BMI ≥30 kg/m2 were considered obese.

Waist circumference (cm) was measured parallel to the midpoint between the lower limit of the 12^{th} costa and the ischial spine. The limits were accepted as >102 cm in men, and >88 cm in women (ATP: adult treatment panel III criteria).

4. Sample collection

Among the 1500 patients visiting the Department of Medicine, Faculty of Medicine, Benghazi University hospital for medical check up, 650 subjects were taken for the study. 200 subjects taken as controls(100 –males; 100-females) and 250 (100-males; 150-females) subjects formed the obese group and 200 formed the diabetes group(100 males and 100 females).Fasting blood samples were collected in vacutainer tubes with a gel separator and in heparinized tubes for HbA1C measurements and were centrifugated at 2000 rpm for 15 min at 4°C after an incubation period of 30 min. All biochemical variables were measured on the same day of the blood collection. Remaining serum specimens were stored at −20°C until analysis of adiponectin, leptin and resistin levels.

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5. Biochemical methods

Serum glucose, total cholesterol (TC), HDL-cholesterol (HDL-C), triglyceride (TG) were measured by an enzymatic colorimetric method.Serum adiponectin levels were measured by enzyme linked immunosorbent assay (ELISA) with a sensitivity of 3 ng/ml. Serum leptin levels were measured by an active human leptin ELISA (DSL, Diagnostic System Laboratories, USA) with a sensitivity of 0.05 ng/ml. Serum resistin levels were measured by ELISA (Linco Research, USA) with a sensitivity of 0.16 ng/ml.

6. Calculations

Low-density lipoprotein-cholesterol (LDL-C) was calculated using the Friedewald formula. Standing height and body weight were measured with the subjects dressed in light indoor clothing without shoes. Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m^2).

7. Statistical analyses

Statistical analysis was performed using SPSS for Windows (Statistical Package for the Social Sciences, version 20.0; SSPS Inc. Chicago, IL, USA). The normal distribution of the variables was evaluated using the Shapiro-Wilk test. The Mann-Whitney U test was used for the comparison of variables which were not normally distributed, and the independent Student's t-test for the comparison of variables which were normally distributed. The Pearson and Spearman tests were used for the evaluation of correlations among the variables according to the distribution of variables. $P<0.05$ was accepted as indicative of statistical significance. The results of variables with a normal distribution were expressed as mean ± SD and those with a non-Gaussian distribution were expressed as median (25th–75th percentile).

8. Ethical considerations

The study was carried out in accordance with the Declaration of Helsinki. Informed consent was obtained from all the patients for the initial study. The protocol was approved by the Medical Ethics Committee of the Faculty of Medicine, Benghazi University, Benghazi,Libya. Additional informed consent was obtained for the present study.

Results: Table.1. shows the differences in waist circumferences reported for various ethnic groups

Country or Ethnic group	Sex	Waist Circumference(cm)
*South Asian	Men	>94
	women	>80
*Chinese	Men	>90
	Women	>80
*Japanese	Men	>90
	Women	>80
*Europid	*Men	>94
	Women	>80
**Libyan	Men	>93
	Women	>90

Source *Adapted from Zimmet and Alberti [2006] [8]; ** present study

Table 1. Ethnic differences in Waist circumferences

Indicator	Cut off Points	Risk of Metabolic complications
Waist circumference	>94cm(M), >80cm(W)	Increased
Waist circumference	>102cm(M), >88cm(W)	Substantially increased
W/H ratio	>0.90(M), >0.85(w)	Substantially increased

M: men; W: women

Table 2. World Health Organization (WHO) cut off points and risk of Metabolic complications[9]

The mean BMI in Libyan adults is reported to be 27.7 kg/m2 (26.4 kg/m2 in men and 29 kg/m2 in women), and the mean waist circumference is 93.3 cm. [10] In the present study compared to other ethnic groups Libyan Men and women have higher BMI and Waist circumference carrying higher risk for metabolic complications as well as for chronic diseases. (BMI 25-30; (29.5) and 30 to 35 (34.5)respectively in normal as well as obese controls). Waist circumference 104cm; 114 cm for normal and obese subjects respectively; Waist circumference to Hip circumference; 0.97 for both men and women subjects.(W/H ratio). The normal control group had higher BMI as well as higher waist circumference indicating both subcutaneous fat and visceral fat are increased in the subjects studied.

	*Chinese	*Malay	*Asian Indian	*Libyan	P Anova
Males-Total Adiponectin(μg/ml)	*3.10±1.79*	*2.97±1.80*	*2.97±1.75*	*1.97±1.05*	*0.01*
Females(Total Adiponectin(μg/ml)	*4.60±2.50*	*4.28±2.52*	*3.83±1.95*	*2.45±1.10*	*0.001*

*Adapted from Chin Meng Khoo et al.[11] ** present study

*P value for comparison between the ethnic groups in men; †P value for comparison between the ethnic groups in women. The values for adiponectin for both Libyan men and women were comparatively lower than the values reported for other ethnic groups like Chinese, Malay, Asian Indian groups.

Table 3. Ethnic variation in Serum Adiponectin levels

	Control-normal	Obese controls	Diabetes	*P-value*	Adjusted P-value
Leptin, ng/mL	13.90 ± 3.16	*28.10 ± 5.00	**32.25±6.50	*0.000 **0.000	P<0.001
Adiponectin, µg/mL	2.01± 1.05	1.90± 0.75	*5.45±1.05	**0.009	P<0.01
Resistin, ng/mL	6.80 ± 3.70	*18.46 ± 8.80	**24.45±9.50	*0.0039 **0.000	P<0.01 P<0.001

Table 4. Serum Adiponectin, Leptin and Resistin levels in normal, obese and Diabetic Libyan patients

The serum levels of adiponectin did not show significant difference in their values between controls and obese subjects.The adiponectin level in diabetic subjects is significantly higher than the control subjects. The serum levels of leptin and resistin were significantly higher for obese and T2DM compared to normal controls.

	Control	Obese	Diabetes	p.value
Body mass index(kg/m^2)	29.5 (25.5-30.0)	*34.5 (30 – 35)	**36.5 (35-37.5)	*<0.001 **<0.001
Waist circumference(cm)	104	* 112	**120	*<0.001 **<0.001
FastingBlood glucose(mg/dL)	89.50±15.50	105.50±20.50	*155.50±24.50	*<0.001
Glycated hemoglobin(%)	5.50±1.05	6.45±1.25	*8.90±1.50	*<0.001
Total Cholesterol (mg/dL)	128.45±18.40	148.20±24.50	*175.50±25.50	*<0.001
HDL-cholesterol(mg/dL	37.45±4.50	35.50±5.50	*32.50±6.50	<0.05
LDL cholesterol (mg/dL)	95.45±12.50	105.5±14.00	*125.00±7.50	*<0.05
Non-HDL cholesterol(mg/dL)	91.00±7.50	*112.70±8.00	*143.00±12.50	<0.05
Triglycerides(mg/dL)	99.50±10.50	105.50±12.00	*145.00±25.50	<0.01

Table 5. Serum glucose, glycated hemoglobin (HbA1c) and Lipid Profile in the Libyan Subjects

There was no marked differences between the control group and obese group with respect to the serum levels of glucose, HbA1c, total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides. There were marked increases in total cholesterol, LDL cholesterol, triglycerides with a marked fall in HDL cholesterol in diabetec subjects (dyslipidemia)

A marked increase was observed in non-HDL cholesterol in obese and diabetics compared to the control group.

The levels of serum total cholesterol and HDL cholesterol are comparatively lower for local Libyan subjects when compared to South Asians and Non South Asians.

	*Non-south Asians	*South Asians	**Libyan	P value
Total cholesterol (mg/dL)	207.60±30.45	199.88±28.45	*128.45±18.40	0.0028 <0.01
HDL cholesterol (mg/dL)	47.55±6.50	41.45±8.50	*37.5.±5.50	0.033 <0.05
Triglcyerides(mg/dL)	145.12±24.50	140.6±25.50	145.5±12.20	0.45

*France et al [12] ** present study

Table 6. Serum lipid profile in different ethnic groups

9. Discussion

Of the anthropometric measures Body mass index (BMI), waist circumference and waist-hip ratio, waist circumference were reported to be more closely related to abdominal obesity and T2DM. Majority of the studies supported the view that there is no optimal cut-off point that can be universally applied. It was suggested that country or region-specific cut off points may be used. [13-14]

Data available in the literature suggest that lower waist circumference and waist-hip ratio cut off point for Asians-85cm and 80 cm, W/H ratio 0.9 and 0.8 for men and women, respectively. [15-17] A study from Tunisia provided a cut-off point for waist circumference (for obesity, diabetes,and CVD) of 85 cm for both men and women, based on sensitivity being equal to specificity.[18]. The values for BMI and WC for Arab Nations are reported to be similar to European population.[19]

Obesity is a major public health concern for Libya. It is reported that about 30% of Libyan adults are obese. About 64% of Libyan adults are either overweight or obese. In the present study BMI values for control subjects were 29.5, 34.5 for obese subjects and 36.50 for T2DM subjects. WC values for control was 104cm,114 cm for obese subjects and 120 for T2DM subjects. These values clearly indicate that majority of the population are either over-weight or obese. This is supported by data that obesity related diseases like type 2 diabetes (T2DM), hypertension, poly cystic ovarian disease (PCOD) are on the rise in Libya. [7, 20-22]. There is a dire need for finding risk markers for obesity and obesity related disorders.

There is a shift in focus to find out whether ethnic diversity could be a factor in the distribution pattern of adiposity variation in different populations. Few studies have stated that adipocytokines particularly adiponectin values differ for different population indicating that adiponectin could be taken as a biomarker of ethnic heterogeneity. When compared to other population serum adiponectin values were comparatively lower for Libyan subjects. Serum leptin and resistin levels were higher for obese and T2DM subjects compared to control ones.Paradoxically the serum levels of adiponectin were higher for T2DM subjects contrary to reports that there is hypoadiponectinemia in T2DM. Hyperadiponectinemia reported quite

contrary to the earlier observations is suggested to be due to the presence of severe insulin resistance possibly to genetically defective insulin receptors. [23]

This finding emphasizes that insulin receptor has a critical role regulating adiponectin synthesis as well as clearance. Patients who have anti-insulin receptor antibodies may be responsible for severe insulin resistance (Type B IR) who show a significant increase in serum adiponectin levels. Such a finding brings out considerable focus on the adiponectin –insulin sensitivity concept. Rather it opens up for more avenues of research to exactly elicit the adiponectin's role in insulin sensitivity and suggests that insulin effect on adiponectin metabolism is undermined.[23]

In the present study T2DM Libyan patients showed marked increase in serum adiponectin levels compared to the control subjects. These subjects had higher insulin levels and insulin resistance shown by HOMA index. The duration of diabetes in these patients is 10 years or more.The results are not shown here.

This finding appears unique to Libyan diabetic subjects. It is reported earlier that adiponectin levels in Libyan subjects are comparatively lower when compared to European or western population in general. Therefore serum adiponectin levels seem to be determined by ethnic heterogeneity reflected by the distribution of adipose tissue and its genetic regulation of adiponectin's synthesis, secretion and degradation. Possibly the reportedly higher BMI in the population with a higher basal insulin levels (accompanied by insulin resistance) might have an suppressive effect on adiponectin formation or clearance.

Insulin resistance(IR) is now generally accepted to be the primary metabolic defect of T2DM [24]. IR is defined as a state that requires more insulin to obtain the biological effects achieved by a lower amount of insulin in the normal state [25].

In contrast to other adipokines, circulating levels of adiponectin correlate inversely with body fat and IR in humans [26] and rodent models [25].). It circulates at high levels in human plasma accounting for approximately 0.01% (0.5-30 μg/mL) of all plasma protein in normal individuals [27], 1000-fold higher than other hormones such as leptin and insulin. Gender has an effect on concentrations of adiponectin, with females having higher levels than males [28]. It is also well known that adiponectin levels increase with age, however the cause for this increase is still unknown [29]

The molecule adiponectin is a 244-amino-acid long adipokine secreted from adipocytes. The gene product is a 30kD protein [30], however this is not found in circulation. Adiponectin automatically self-binds to form larger structures and there are different multimeric forms including low molecular weight (LMW) trimers, middle molecular weight (MMW) hexamers, high molecular weight (HMW) oligomeric structures and finally globular adiponectin (gC1q domain)[27]. It has been proposed that this globular fragment is generated by proteolytic cleavage of adiponectin multimers by leukocyte elastase secreted from activated monocytes and/or neutrophils [24]; however the pathophysiological importance of this cleavage remains to be determined. Structurally, the globular form of adiponectin lacks the collagenous domain necessary for multimerization. Adipocytes secrete both the low-molecular weight and high-molecular weight forms of adiponectin in vivo and in vitro. Thus, the low-molecular weight

and high-molecular weight forms of adiponectin are the predominant forms in serum whilst smaller complexes such as the trimer are virtually undetectable. [31].

10. Monomeric structure

There are four distinct regions of adiponectin. The protein starts with a short signal sequence which acts to target the hormone for secretion outside the cell, then it leads into a short region that is variable between species, followed by an amino-acid region that shows similarity with collagenous protein, and finally ending with a globular domain. The three dimensional structure of its C-terminal globular domain is similar to that of tumor necrosis factor–alpha (TNF-α), even though there is no sequence homology at the primary structure level. [32].

11. Higher order structures

Initially, three adiponectin molecules associate through disulphide bonds within the collagenous domains of each monomer to form bouquet-like higher order structure, a homotrimer. The trimers continue to self-associate and form hexamers [33].

The levels of the higher order structures are sexually dimorphic [34], where females have increased proportions of the high-molecular weight forms. The varying forms have altered biological activity and therefore may also have separate functions. The gC1q domain and the trimeric forms of adiponectin activate AMP Kinase in skeletal muscle and lead to increased fatty acid oxidation and reduction in glucose concentrations, whereas the hexameric and full length HMW forms are thought to activate nuclear factor kappa B (NF-κB) pathways [35]. The proportion of HMW adiponectin within adipose tissue is higher than in blood plasma, suggesting regulation at the level of secretion and is a mechanism of adiponectin complex distribution. All isoforms of the molecule are stable in circulation having a relatively longer half life (half-life of ~15hrs) [24].

12. Receptors and signaling

Two receptors have been identified that bind adiponectin: Adipo R1 and Adipo R2. AdipoR1 was first identified when encoding cDNA was isolated from human skeletal cDNA library by screening for adiponectin binding [36]. The AdipoR2 was identified later due to its striking homology to AdipoR1. Both are surface membrane proteins [36] and have homology to G protein-coupled receptors.. These receptors contain seven transmembrane domains, but are structurally and functionally distinct from other known GPCRs (G-protein-coupled receptors[37]. The receptors have different affinities to the various molecular forms of adiponectin. AdipoR1 and AdipoR2 are found in liver, muscle and adipose tissue in humans; however AdipoR1 is predominantly expressed in skeletal muscle whereas AdipoR2 is more predomi-

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nant in the liver [36]. AdipoR1 is a high-affinity receptor for globular adiponectin as well as having a lower affinity for full length adiponectin. In contrast the AdipoR2 receptor has an equal intermediate affinity for globular and full length HMW adiponectin [36]. The receptors affect a very important cellular metabolic rate control point, by targeting AMP-activated protein Kinase (AMPK), downstream. AMPK is a stress induced kinase that is activated in response to depleting Adenosine triphosphate (ATP) or increasing Adenosine monophosphate (AMP) levels. AMPK activates ATP and generates catabolic processes such as fatty acid breakdown and glycolysis and shuts down ATP-consuming processes such as lipogenesis [37]. Expression of these receptors is correlated with insulin levels [24]. A review of studies involving the adiponectin receptors suggests that they may have an important role in adiponectin physiology. Key findings suggest that changes in expression of AdipoR isoforms in skeletal muscle (rather than total circulating adiponectin concentrations) may be of physiological importance [38]. More recently, by means of expression cloning, T-cadherin has been recognized as an adiponectin receptor on vascular endothelial cells and smooth muscle [36]. The expression of this cadherin molecule is known to be correlated with atherosclerosis [33].By genomic sequence analysis, Saito et al. determined that the ADIPOQ gene spans 16 kb,contains 3 exons and 2 introns and the promoter lacks a TATA box(a sequence involved in the process of transcription). The exon-intron organization of this gene was very similar to that of obese gene,encoding leptin. Saito et al. reported that the ADIPOQ gene was located on human chromosome band 3q27using chromosome mapping of this gene by fluorescence in situ hybridization (FISH) taking genomic DNA fragment as a probe [39]. It is reported that a mutation in this gene is associated with low serum adiponectin levels and T2DM[41].

It has been reported that blood concentrations of adiponectin fall from 20-50% in humans and mice respectively with the administration of insulin, thus implying that the effect of insulin to lower adiponectin levels may involve inhibition of adipocyte secretion. Plasma adiponectin levels have also been shown to be decreased in an obese rhesus monkey model that frequently develops Type 2 Diabetes [42] Many prospective studies [43-45] have shown that lower adiponectin levels are associated with a higher incidence of diabetes in humans and more importantly the decrease in plasma adiponectin levels was in parallel with the decrease in insulin sensitivity [25]. This finding is further supported by a recent analysis of 13 prospective studies, which found that higher adiponectin levels were associated with a lower risk of Type 2 Diabetes across diverse populations [45-46].

The levels of serum total cholesterol and triglycerides are comparatively lower for local Libyan subjects when compared to South Asians and Non South Asians.[47] The serum level of total HDL cholesterol is also low in Libyan subjects probably due to the lowered levels of total cholesterol and triglycerides.[47].

A marked increase was observed in non-HDL cholesterol in obese individuals compared to the control group.[48] and there was a marked fall in HDL cholesterol indicating that dyslipidemia is prevalent in local Libyan subjects

This preliminary study indicates that the distribution of fat in Libyan population varies from other populations. There is a marked increase in total as well as abdominal adiposity indicated by anthropometric measurements. The serum level of adiponectin is low in this population

along with comparatively HDL cholesterol with a marked increase in non-HDL cholesterol. Therefore further studies are being carried out to bring out the nature unique ethnic diversity in the population as well as to recommend that an overall reduction of body weight in the population need to be considered to lower risk of metabolic disorders.

Apart from these observations the serum levels of adiponectin were found to be lower for the Libyan subjects and its level was increased in T2DM subjects.

This observation seems to suggest whether serum adiponectin level in Libyan subjects can be taken as a biomarker of ethinic heterogeneity.

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The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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