

# Association of Hyperhomocysteinaemia with Hyperglycaemia, Dyslipidaemia, Hypertension and Obesity

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## Abstract

There is conflicting scientific data about the link between, high homocysteine (Hcy) levels in the general population, and obesity. This is a case-control study aimed to assess the role of hyperhomocysteinemia in obesity and its associated illnesses, including hypertension, dyslipidemia, and hyperglycemia in Gezira state, Sudan. Two hundred and eleven participants were included in the study, 140 were obese (117 females and 23 males) and 71 were normal weight control, the obese median age was  $49.49 \pm 12.2$  years. The control group consisted of 71 individuals with an average age of  $45.78 \pm 17.67$  years. Among those who were already known to be obese, 67 (47.9%) reported having type II diabetes mellitus, 71 (50.7%) reported having hypertension, and 35 (25%) were obese without having either diabetes or hypertension. Three mls of venous blood from each participant were collected in the morning after a 12 h overnight fasting in Lithium heparin containers then the plasma was separated and stored at  $-80^{\circ}\text{C}$  for analysis. Serum Hcy and lipid profile were measured using the enzymatic method by Cobas C 411 analyzer. In comparison to obese non-hypertensive, the results showed that obese hypertensive with Hcy levels  $> 15$  mol/L had a considerably increased risk (OR 1.12). When Hcy levels  $> 15$  mol/L were compared to obese diabetics and obese non-diabetics, insignificant difference was shown (P: 0.345). Males had a higher likelihood of having hyperhomocysteinemia than females did (OR 1.2). Homocysteine, cholesterol triglyceride, LDL, and HDL mean values were compared between case and control groups using the independent sample t-test, and the results revealed statistically significant (P:  $<0.05$ ). Relationships between hyperhomocysteinaemia and cholesterol, triglycerides, LDL, and HDL in the group of obese individuals were not statistically significant (P:

0.574, 0.265, 0.748, and 0.14), respectively. Obesity and Hcy concentrations were shown to be substantially correlated. However, there was no statistically significant association between baseline plasma Hcy levels and hyperglycemia, hypertension, or dyslipidemia.

## Keywords

Homocysteine, Hyperglycaemia, Dyslipidaemia, Hypertension, Sudan

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## 1. Introduction

Obesity is a global issue that has been connected to changes in the physiological function of adipose tissue. More than half of the world's population will be obese by 2030 [1]. The fact that obesity is unequal, some are metabolically healthy meaning they do not have any additional metabolic disturbance, but most are metabolically unhealthy. Slight, and progressive, differences in glucose tolerance, inflammatory response, adipose tissue distribution, pattern of adipokine secretion, and age may contribute to this phenomenon. Age-related increases in obesogenic variables are anticipated to make obesity more common in middle-aged and elderly people. As a result, the majority of co-morbidities related to obesity is common to aging and may have similar basic processes [2].

Obesity and nutritional deficiency or excess lead to endoplasmic reticulum (ER) stresses resulting in secretion of impaired unfolded protein. ER dysfunction and the consequence of unfolded protein have a role in inducing metabolic disturbance [2]. Mitochondria regulate apoptosis by the intrinsic pathway triggered in response to cellular stress signal and apoptosis regulatory proteins [3]. Apoptotic proteins level are increased in adipocyte of obese human, therefore excess food can cause mitochondrial dysfunction and susceptibility to apoptosis which improve metabolic syndrome [4]. Mitochondrial defect lead to cellular oxidative damage caused by generation of reactive oxygen species (ROS) that exceed the natural antioxidant is an initiating factor in metabolic disturbance [2].

Hcy is a sulfur containing amino acid, form in the cytoplasm during intracellular metabolism of methionine. Within the methionine cycle, methionine is converted to s-adenosylmethionine (SAM) which acts as methyl donor. S-adenosylhomocystine (SAH) is formed following methyl donation by SAM and Hcy formed through liberation of adenosine from SAH by enzyme SAH hydrolase. Due to the reversal physiologic reaction of s-adenosylhomocystine hydrol Hcy accumulation leads to synthesis of s-adenosylhomocystine which is stronger inhibitor of s-adenosylmethionine dependant transferase that methylate abroad spectrum of cellular component (lipid, DNA and protein) [5].

Hcy a sulfurous-amino acid is crucial for the metabolism of methionine and folate. Hyperhomocysteinemia is the term for a condition where there is an abnormally high level of Hcy in the plasma (above 15 mol/L) (HHcy). Increased

total plasma homocysteine (tHcy) is regarded as harmful for cells and is linked to a variety of health issues such as obesity, metabolic syndrome and cancer [6].

Several possible mechanisms can explain the relationship between Hcy concentrations and obesity, according to a meta-analysis study conducted by Wang *et al.* first, higher Hcy levels were linked to lipid accumulation in tissues, resulting in obesity. Second, Hcy induced endoplasmic reticulum stress induces deregulation of the cholesterol and triglyceride biosynthesis pathways, causing lipids to be not processed correctly. Third, obesity is recognized as a chronic inflammatory condition. In this view, elevated inflammatory markers (such as CRP and fibrinogen) were observed to be related with Hcy levels. Finally, visceral adipose tissue impairs various hepatic activities via the portal by disrupting the proper functioning of enzymes that remove. However, it is still unknown what causes obese to have higher Hcy [7].

Each extra unit of Hcy concentration above 14 mol/L in diabetic patients was discovered to be associated with an increased risk of diabetic retinopathy and renal failure [6]. By interfering with insulin receptor phosphorylation and therefore influencing the downstream signaling cascade, it has been demonstrated that Hcy reduces insulin signaling. A rise in the production of the adipose tissue peptide hormone resistin also coincided with the signaling problem. Obesity and resistin have both been related to diabetes in the past [8].

Increased risk is shown in obese patients with aberrant lipid profiles and Hcy, which increases cardiovascular morbidity and mortality in type II diabetes mellitus, particularly if it was coupled with hypertension [9]. According to recent studies, the link between Hcy levels and MetS components, notably systolic blood pressure, increases the risk of cardiovascular disease (CVD) [10].

When Hcy oxidation is aberrant, the endothelium becomes injured because it is unable to break down Hcy. Hcy undergoes auto oxidation at high Hcy levels. This process takes place in plasma and produces ROS that damage cells' oxidative defense mechanisms and are harmful to endothelial cells. Vascular cell adhesion molecule and monocyte chemo attracted protein are released as a result of oxidized LDL. The first lesion in atherosclerosis is a fatty stripe caused by the conversion of the monocyte into a macrophage, which then absorbs the oxidized LDL [11]. Hcy may promote CVD by a number of ways, including an increase in muscle cell proliferation that narrows blood arteries, changes to blood coagulation factors, oxidative harm to the vascular endothelium, and damage to arterial walls [12].

In hypertension, the artery walls thicken and the blood flow resistance rises. As a result, the heart beats more quickly and the blood pressure leaving the heart increases. Due to the lack of early symptoms, high blood pressure is referred to as the silent killer. Only when an organ in the body is inflamed or harmed can the effects of elevated blood pressure become apparent [8]. By inhibiting the nitrogen oxide-induced vasodilation, encouraging the proliferation of vascular smooth cells, and altering the elastic properties of the vascular wall, Hcy causes

oxidative damage to the vascular endothelium, which results in hypertension [13].

The current study's hypothesis was that elevated plasma Hcy concentrations are linked to obesity and its associated illnesses, including hypertension, dyslipidemia, and hyperglycemia.

## **2. Material and Method**

### **2.1. Study Design and Participants**

This was a case-control research conducted in Gezira state in a period between 2019 until 2022 with 140 obese as the case and 71 normal weight as the control. Participants were recruited by trained field workers and gave their written consent voluntarily.

### **2.2. Ethical Consideration**

IRB in the faculty of medical laboratory science at the University of Gezira provided ethical approval for this work. All participants signed a standard informed consent form.

### **2.3. Data Collection Tools**

A questionnaire was utilized to collect data on demographics, lifestyle, and health concerns such diabetes, hypertension, obesity, renal disease and, kidney disease, and heart disease.

### **2.4. Physical Examination**

All of the participants underwent a physical examination as well as laboratory tests. The patient's height and weight were measured during the physical examination. The participants' body weight was assessed while they wore light clothing and wore no shoes. In an upright position, the height was measured without shoes. BMI was computed by multiplying a person's weight in kilograms by their height in meters squared. BMI of less than 25 were considered normal weight, while those with a BMI of 30 or more were considered obese.

### **2.5. Laboratory Tests**

In a lithium heparin container, three ml of venous blood samples for Hcy and lipid profile (cholesterol, triglyceride, low density lipoprotein, high density lipoprotein) measurement were collected and centrifuged immediately. Plasma was isolated and kept at  $-20$  degrees Celsius. The concentration of plasma Hcy was determined using an enzymatic technique on a Cobas c311 analyzer. The normal reference range was up to 15  $\mu\text{mol/L}$ . The diagnostic criteria used for the parameters were follows: hyperhomocysteinemia = blood Hcy  $> 15 \mu\text{mol/l}$ , hypercholesterolemia = blood cholesterol  $> 5.7 \text{mmo/l}$ , hypertriglyceridemia = blood triglyceride  $> 2.26 \text{mmol/l}$ , obesity = BMI  $> 30 \text{kg/m}^2$ .

## 2.6. Statistical Analysis

The data was analyzed using version 18 of the Statistical Package for Social Science (SPSS). Descriptive statistics were calculated for the data in the form of mean and standard deviation ( $SD \pm$ ) for quantitative data and frequency and distribution for qualitative data. In the statistical comparison between the different groups, the significance of difference was tested using Student's t-test that used to compare mean of two groups of quantitative data and inter-group comparison of categorical data was performed by using chi square test ( $X^2$ -value) and fisher exact test (FET). The association of hyperhomocysteinemia ( $>15.0$  mol/L) with obesity, as well as related metabolic disease such as hypertension and diabetes, was reported as odds ratios (OR) obtained by separate logistic regressions for each outcome variable, with age and gender adjustment. Using multiple logistic regressions, we calculated the OR for the combined risk against hyperhomocysteinemia.

## 3. Results

The study involved 211 participants, of whom 140 were obese (23 men and 117 women) had a median age of  $49.49 \pm 12.2$ . There were 71 people in the control group whose average age was  $45.78 \pm 17.67$  years. According to socio demographic information, the distribution of the study population is presented in (Table 1).

Among those who were known to be obese, 67 (47.9 percent) reported having type II diabetes mellitus, 71 (50.7 percent) reported having hypertension, and 35 (25 percent) were fat without either diabetes or hypertension (Table 2).

17 (or 42.5%) of the 67 (47.9%) obese diabetic patients were hyperhomocysteinaemic. 23 participants, or 57.5 percent, of the 71 obese and hypertensive subjects were hyperhomocysteinaemic. After stratification according to tHcy levels, the frequency of diabetes and hypertension among study participants was compared using the chi square and Fisher's exact tests. The results showed that obese hypertensive with tHcy levels  $> 15$  mol/L had a significantly higher risk (OR 1.12) compared to obese non hypertensive. When compared to obese diabetics and obese non-diabetics, with tHcy levels  $> 15$  mol/L demonstrated in significant difference ( $P: 0.345$ ). Males were more likely than females to have hyperhomocysteinemia (Table 3) and (Table 4).

The independent sample t-test was used to compare the mean values of Hcy, cholesterol triglyceride, LDL, and HDL in case and control, and the results showed statistically significant ( $P < 0.05$ ) increases in these markers. However, there were statistically significant ( $P < 0.05$ ) drops in the mean HDL levels in the same group (Table 5).

In the group of obese people, the relationships between hyperhomocysteinaemia and cholesterol ( $P = 0.574$ ), triglycerides ( $P = 0.265$ ), LDL ( $P = 0.748$ ), and HDL ( $P = 0.14$ ) were not statistically significant (Table 6).

**Table 1.** Frequency, percentage and average of Socio-demographic data.

		Case (N = 140)		Control (N = 71)	
		F	%	F	%
<b>Gender</b>	<b>Male</b>	23	16.4	20	28.2
	<b>Female</b>	117	83.6	51	71.8
<b>Age Group</b>	<b>20 - 40 Years</b>	33	23.6	38	53.5
	<b>41 - 60 Years</b>	84	60.0	22	31
	<b>61 - 80 Years</b>	23	16.4	11	15.5
<b>Age/years</b>		49.49 ± 12.2		45.78 ± 17.67	

**Table 2.** Frequency and percentage of the disease presence in obese group.

		Case (N = 140)	
		F	%
<b>Hypertensive</b>	<b>Yes</b>	71	50.7
	<b>No</b>	63	45.0
<b>Diabetes</b>	<b>Yes</b>	67	47.9
	<b>No</b>	67	47.9
<b>Hypertensive + Diabetes</b>	<b>Both of them</b>	39	27.9
	<b>One of them</b>	60	42.9
	<b>None of them</b>	35	25

**Table 3.** Frequency and percentage of Hcy in diabetes and hypertension.

		Hypertension		Total	Diabetes	
		Yes	No		Yes	No
<b>Hyperhomocysteinemia</b>	<b>Count</b>	23	17	40	17	23
	<b>%</b>	57.5	42.5	100%	42.5	57.5
<b>Normal Hcy level</b>	<b>Count</b>	48	46	94	50	44
	<b>%</b>	51.1	48.9	100%	53.2	46.8
<b>Total</b>	<b>count</b>	71	63	134	67	67
	<b>%</b>	53	47	100%	50.0	50.0

**Table 4.** Odds Ratio, confident interval and significant difference for hyperhomocysteinemia in hypertension, diabetes and gender.

		Odds Ratio	Confident interval	P-value
<b>Hypertension</b>	Yes	1.12	0.808 - 1.569	0.572
	No	0.86	0.573 - 1.316	
<b>Diabetes</b>	Yes	0.79	0.532 - 1.201	0.345
	No	1.22	0.872 - 1.730	
<b>Gender</b>	Male	1.20	0.552 - 2.623	0.63
	Female	0.96	0.815 - 1.137	

**Table 5.** Association between Hcy and lipid profile in case and control.

			Mean	STD	P-value
<b>Homocysteine</b>	Obese	140	12.65	4.9	<b>0.002</b>
	Control	50	10.45	3.8	
<b>Cholesterol</b>	Obese	140	184.64	56.9	<b>0.000</b>
	Control	71	150.73	37.5	
<b>Triglyceride</b>	Obese	140	252.05	151.0	<b>0.000</b>
	Control	71	135.82	79.0	
<b>LDL</b>	Obese	140	99.91	61.8	<b>0.021</b>
	Control	71	85.15	29.9	
<b>HDL</b>	Obese	140	37.76	9.9	<b>0.023</b>
	Control	71	40.99	9.5	

**Table 6.** Association of Hcy level and lipid profile in obese group.

	Pearson Correlation	Sig. (2-tailed)
<b>Cholesterol</b>	-0.041	0.574
<b>Triglyceride</b>	0.081*	0.265
<b>LDL</b>	-0.023**	0.748
<b>HDL</b>	-0.106	0.144

#### 4. Discussion

There is a considerable knowledge gap about Hcy, including the patterns of Hcy concentrations in populations, the impact of gender on Hcy levels in the blood, and the physiological processes that Hcy impacts. The current study's findings indicated that men had a higher risk of hyperhomocysteinemia than women did (odds ratio were 1.20). Previous Studies have shown that males have higher concentrations of Hcy than females, but the difference disappears after menopause. Studies have also suggested possible associations between Hcy and a number of endogenous sex hormones also have been discovered that high Hcy levels were negatively associated females' cardiovascular health but not to males. This shows that there are differences in both the variables affecting Hcy in males and females as well as the impacts on the body, which is quite intriguing and merits more research [14].

In this investigation, odds ratios OR and their associated 95% confidence intervals (95% CIs) were used to assess the relationship between Hcy levels and hypertension (HTN) (OR [95% CI] = 1.12 [0.808 - 1.569], P = 0.572). Although the authors discovered that 57.5% of their hypertensive participants had hyperhomocysteinemia, the association between plasma Hcy and the risk of hypertension was statistically insignificant after age and gender adjustments. Numerous studies suggested that patients with hypertension had higher levels of Hcy than those who did not. Other epidemiological studies have investigated the connec-

tion between the polymorphism and HTN, however the outcomes were controversial. Retrospective studies revealed a strong connection. However, after adjusting for known risk factors, a meta-analysis of prospective studies discovered that a 25 percent lower usual Hcy level—which can be achieved in many populations by fortifying cereals with folic acid—was only linked to an 11 percent (95 percent CI 4 percent - 17 percent) lower CHD risk. The lower confidence limit's weak relationship, though significant, may or may not be entirely non-causal [15].

Hcy levels were measured in 67 hyperglycemic individuals for the current study, although there was no statistically significant correlation ( $P = 0.345$ ). 17 (42.5%) of the hyperglycemic individuals had elevated Hcy levels. Various results about the relationship have been reported. In their investigation of the association between Hcy and hyperglycemia, Vayá *et al.* discovered a weak correlation [15]. According to Elias and Eng, Shaikh *et al.*, and other researchers, Hcy levels in diabetes mellitus can be either low or high. The findings of Mishra *et al.* and Akali *et al.* who discovered elevated Hcy levels in diabetes individuals are at odds with the results of our study. High Hcy levels were discovered to be a significant risk factor in diabetes patients. The research by Shaikh *et al.* provided evidence in favor of this work [13].

When compared to control, Hcy was significantly higher in the obese group. According to a meta-analysis research, obese patients had mean Hcy levels that were higher than those of non-obese patients. The results from the Mendelian randomization method supported the theory that the enhanced risk of obesity was plausibly influenced by the increased Hcy levels [16]. The levels of Total Cholesterol, Triglycerides, and LDLc were significantly higher in the obese group, while the levels of HDLc were significantly lower when compared with control group. These supported the assertion made by GeraLd H, *et al.* [17] that low HDLc is a well-recognized independent and potent predictor of atherosclerosis [17]. In the present study hyperhomocysteinaemia and cholesterol ( $P = 0.574$ ), triglycerides ( $P = 0.265$ ), low LDL-C levels ( $P = 0.748$ ), and HDL-C ( $P = 0.144$ ) were not found to be statistically significantly associated. The results of Vayá *et al.* supported the insignificant relationship. However, Nabipour *et al.* discovered a strong correlation between high Hcy levels and reduced HDL cholesterol [13].

It is important to note the study's shortcomings. First, the study population evaluation was based on a single sample of total Hcy taken at baseline where it is correct to assume that Hcy levels, particularly free Hcy levels, may have an impact on results, second researchers unable to demonstrate a temporal or causative link between Hcy and obesity due to the retrospective case control research design, and also determine the impacts of the risk factors, only qualitatively.

## 5. Conclusion

Hcy concentrations and obesity were shown to be significantly associated. The



study supported the idea that there is a tangential relationship between plasma Hcy and obesity. The correlation between baseline plasma Hcy levels and hyperglycemia, hypertension, and dyslipidemia was not statistically significant, though. Better and more trustworthy results would likely come from a study examining the relationship between plasma Hcy levels and hyperglycemia and hypertension a few days after treatment discontinuation. Unfortunately, it could be dangerous to stop treating diabetics.

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### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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