

## The Correlation between LDL-C and Non-HDL-C Levels and Cardiovascular Events in Patients with Metabolic Syndrome

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### Abstract

In 1988 Reaven described polymorphic metabolic abnormalities involving the incidence of insulin resistance with compensatory hyperinsulinemia, type 2 diabetes mellitus, arterial hypertension and hypercholesterolemia also known as Reaven's syndrome or syndrome X. The aim of the study was to evaluate if cardiovascular risk in patients with metabolic syndrome [MetS] correlate with LDL-C and non-HDL-C levels. The study was a prospective, two-center screening study of 36-month duration located in University Hospital No.1 in Bydgoszcz, Poland and District Hospital in Wąbrzeźno, Poland. The study included 906 participants (460 females [F], 446 males [M], aged 32-76 years), with a confirmed diagnosis of metabolic syndrome according to the 2005 IDF criteria. The study showed that LDL-C and non-HDL-C levels are connected with increased level of triglycerides and impaired fasting glucose. Levels of LDL-C and non-HDL-C also influenced hypertension and hypoalbuminemia to a lesser extent and exerted the least influence in individuals with type 2 diabetes mellitus. The study proved that the components of metabolic syndrome, especially abdominal obesity, hypertriglyceridemia, and impaired fasting glucose have a major impact on the level of LDL and non-HDL-C, which is associated with a higher cardiovascular risk.

**Keywords:** Metabolic syndrome; LDL-C; Non-HDL-C; Cardiovascular risk; Hypertension; Type 2 Diabetes mellitus; IDF

### Introduction

In 1988 Reaven described polymorphic metabolic abnormalities involving the incidence of insulin resistance with compensatory hyperinsulinemia, type 2 diabetes mellitus, arterial hypertension and hypercholesterolemia also known as Reaven's syndrome or syndrome X [1,2]. Today the World Health Organization [WHO] defines this cluster of conditions as metabolic syndrome [3,4]. It is estimated that 20-25% of human population meet the diagnostic criteria for metabolic syndrome [1] with the aforementioned figure constantly increasing. There are numerous modifiable risk factors for cardiovascular disease including dyslipidemia.

The aim of the study was to evaluate if LDL-C and non-HDL-C levels depend on specific abnormalities involving in the metabolic syndrome [MetS] and if cardiovascular risk in patients with metabolic syndrome correlate with LDL-C and non-HDL-C levels. Furthermore, to determine the likelihood of hospitalization connected with cardiovascular diseases [CVD] and death dependent on the various disturbances observed in metabolic syndrome during 36-month period.

### Material and Methods

The study was a prospective, two-center screening study of 36-month duration located in University Hospital Number one in Bydgoszcz, Poland and District Hospital in Wąbrzeźno, Poland. The study included 906 participants (460 females [F], 446 males [M], aged 32-76 years), with a confirmed diagnosis of metabolic syndrome

according to the 2005 IDF (International Diabetes Federation) criteria. Participants were required to meet at least 3 of the 5 criteria. The list of criteria is presented in Table 1.

Abdominal obesity [cm]	F ≥ 80 M ≥ 94
Arterial hypertension (HT) [mmHg]	≥130/85 or treated for arterial hypertension
Triglycerides (TG) [mg/dl]	≥150 [1.7 mmol/l] or treated for dyslipidaemia
HDL-C [mg/dl]	<50 [1.3 mmol/l] in women and <40 [1.0 mmol/l] in men
Fasting glycaemia [mg/dl]	≥100 [5.6 mmol/l] or treated for diabetes

**Table 1:** IDF criteria of metabolic syndrome.

Anthropometric measurements including: height, weight and waist circumference were obtained in all participants (Table 2). As well as blood pressure and Body Mass Index (BMI) measured using the metric system. BMI was calculated as body weight (in kilograms) divided by the square of body height (in meters). Finally, the following demographic factors: age, sex, obesity were determined. Systolic and diastolic blood pressures were measured in the sitting position after 15 min of rest using a sphygmomanometer in both upper extremities. An average of both measurements was calculated. Arterial hypertension was diagnosed according to the IDF definition (RR ≥ 130/85 mmHg). Levels of fasting total plasma cholesterol (TC), triglycerides (TG), high-density-lipoprotein cholesterol (HDL-C) and fasting blood glucose (FBG) were evaluated in all patients. Low-density-lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula. Non-high-density-lipoprotein cholesterol (non-HDL-C) was figured

on the base of formula:  $TC - HDL-C$ . In patients with abnormal fasting glycaemia values and waist circumference  $>80$  cm in women or  $>94$  cm in men, an oral glucose tolerance test (OGTT) was performed to determine glycaemia in the fasting state and 2 hours after the administration of 75 g glucose.

	n	Age (years)	BMI (kg/m <sup>2</sup> )	WC (cm)	SBP (mmHg)	DBP (mmHg)
Female	460	55.2	29.2	89.2	145.6	93.6
Male	446	56.4	31.2	103.1	144.8	95.2
Total	906	55.7	30.1	95.3	145.2	94.4

**Table 2:** The characteristics of the study population.

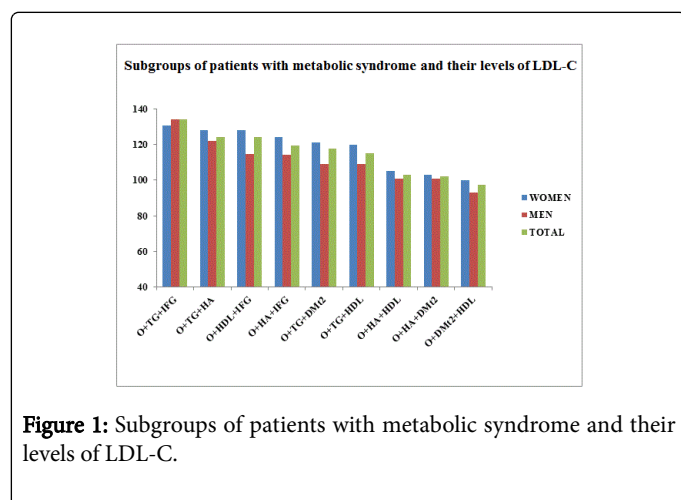
Venous blood samples were collected from fasting patients for biochemical analyses (morphology, ionography, creatinine, BUN, glucose, TSH, cortisol diurnal rhythm, PSA [in men], CRP, fibrinogen). Abnormal results excluded the patient from the study.

Exclusion criteria: a history of heart surgery or other cardiovascular interventions, congenital defects of the heart, cardiac rhythm disorders, pregnancy, chronic kidney disease, electrolyte disorders, inflammation, anaemia, prostate disease and Cushing's syndrome.

All patients, or their families, were contacted by telephone in order to collect medical history information regarding hospitalization for cardiovascular causes and possible deaths, at 12, 24 and 36 months. Statistical analysis was performed using the Statistica 8.0 software (Statsoft Poland, Bydgoszcz). The results were expressed as mean of  $\pm$  standard deviation (SD). The ANOVA rang Kruskal-Wallis test was used for comparison. The results were considered statistically significant when  $p < 0.005$ . The study was approved by the Bioethics Committee of Ludwik Rydygier Collegium Medicum in Bydgoszcz, Nicolaus Copernicus University in Torun, preceding its commencement.

## Results

The study showed that LDL-C and non-HDL-C levels are connected with increased level of triglycerides and impaired fasting glucose.



Levels of LDL-C and non-HDL-C also influenced hypertension and hypoalphalipoproteinemia to a lesser extent and exerted the least

influence in individuals with type 2 diabetes mellitus (Figures 1 and 2). The study also indicated there was no relation between gender and lipid abnormalities.

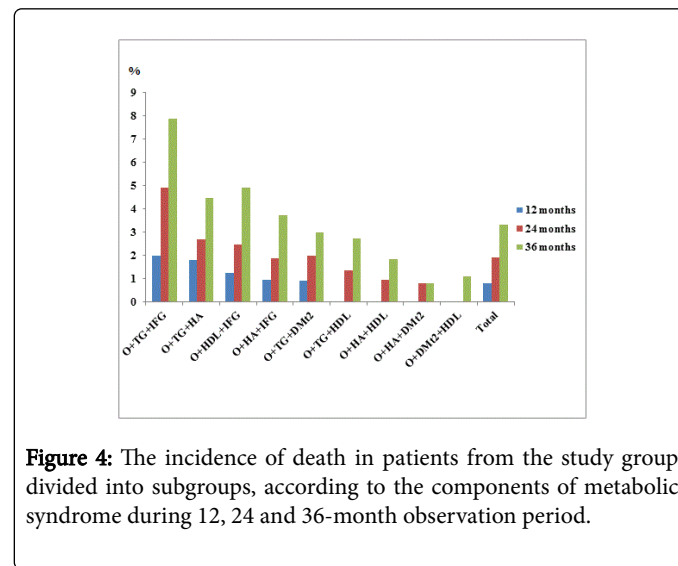
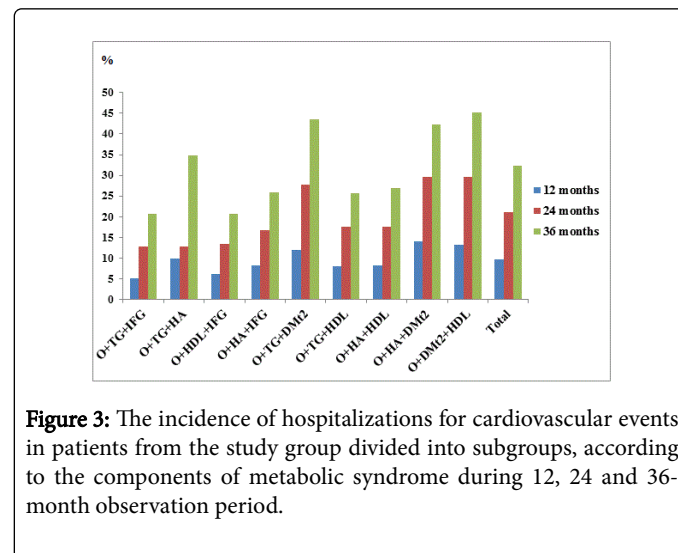
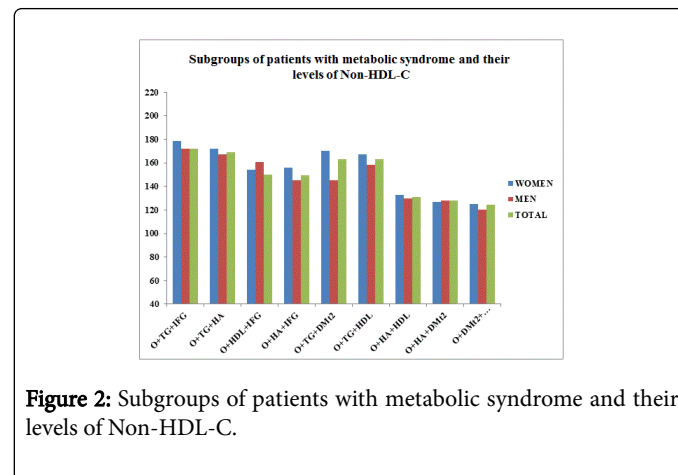


Figure 3 shows the incidence of hospitalizations for cardiovascular events and Figure 4 shows death in patients from the study group divided into subgroups, according to the components of metabolic syndrome during 12, 24 and 36-month observation period.

## Discussion

Cardiovascular disease (CVD) due to atherosclerosis of the arterial vessel wall is the leading cause of premature mortality in Europe [5,6]. The causes of cardiovascular disease are multi-factorial and relate to modifiable lifestyle factors including: tobacco smoking, lack of physical activity and dietary habits. The 2010 International Obesity Taskforce analysis estimated that 475 million adults worldwide are obese, with the number rising to 1 billion if overweight adults are taken into account as well [7]. The WHO considers obesity to be a “21<sup>st</sup> century epidemic” [8]. Obesity leads to hyperinsulinemia even after appropriate adjustment for insulin resistance, and it precedes changes in components of the metabolic syndrome [9]. Perhaps this could be the cause of the decrease in human life expectancy, which is diminishing for the first time in many decades [10]. A relation between obesity and other cardiovascular risk factors, such as age, male gender, diabetes mellitus, hypertension and dyslipidemia, is well known [11,12]. Elevation of TC and LDL-C has received most attention, because these factors be modified by lifestyle changes and drug intervention. Many multiple randomized controlled trials (RCTs) show that reducing TC and LDL-C can prevent CVD, a primary target of pharmacological intervention [5]. There is also a clear association between hypercholesterolemia and the increased incidence of ischemic heart disease [13]. Jousilahti et al. [14] in their study showed that in a population aged 30-59 years, the risk of death from coronary heart disease (CHD) among the participants with cholesterol  $\geq 8.0$  mmol/l (309.4 mg/dl) was five-fold that of the participants with cholesterol  $\leq 5.0$  mmol/l (193.3 mg/dl). Moreover, Engstrom et al. [15] determined that hypercholesterolemia [ $\geq 6.5$  mmol/l (251 mg/dl)] was associated with an increased incidence of cardiac events. A meta-analysis of 61 prospective studies which encompassed 900,000 participants between the ages of 40-89 years found an association between 1 mmol/l (38.7 mg/dl) lower total cholesterol (TC) with about one-half, one-third, and one-sixth lower ischemic heart disease mortality at ages 40-49, 50-69, and 70-89 years, respectively [16].

During the 11-year follow-up of the Atherosclerosis Risk in Communities (ARIC) study population, the increase in CHD risk associated with the presence of the metabolic syndrome at baseline was 1.7-fold in men and 2.6-fold in women and the increase in the risk of stroke was 2.1-fold in men and 2.4-fold in women [17,18]. Lakka et al. [19] showed in middle-aged men in Finland approximate greater risks for CHD death, CVD death, and total mortality for those with MetS. Additionally, Isomaa et al. [20] used the WHO definition to show higher CVD and overall mortality in adults with MetS in Finland and Sweden. In the current study the observations show that in patients with metabolic syndrome, who often belong to the groups of high or very high total cardiovascular risk, this risk of death increases with the increase in LDL-C, so to the same extent as in the general population.

In patients with metabolic syndrome also other factors appear to predispose individuals to premature CVD. Maralani et al. [21] evaluated 3086 residents aged 49 years with MetS defined by International Diabetes Federation criteria. Using Cox proportional hazards and competing risks models with MetS as a time-dependent covariate, they estimated the effect of MetS on CHD mortality: 2-year: 0.46 [0.20-1.03]; 5-year: 0.70 [0.41-1.21]; 10-year: 1.62 [1.02-2.59].

Individual MetS components may have different effects on mortality. While hypertension [22], hyperglycemia [23,24], low HDL-C [23,24] and high triglycerides levels [25] have been shown to predict all-cause and CVD-death, there is inconsistency with regards to which of these MetS components better predicts mortality [21]. It remains unclear whether MetS as a whole or its individual components provide a better prediction of all-cause and cause-specific mortality [21]. No studies have clarified whether earlier or most updated status of MetS best predicts all-cause and cause-specific mortality. Analysis showed that different MetS components were associated with different causes of death [21]. Triglyceride levels were the best single predictor of all-cause and cause-specific mortality in the elderly Australian population [21]. Hunt et al. [26] ascertained that in NCEP-MetS components predicting cardiovascular mortality were IFG, abdominal obesity, and HBP. The results of this study were consistent with the aforementioned literature, which showed the increased risk of death from cardiovascular causes in patients with metabolic syndrome which including hypertriglyceridemia, arterial hypertension and impaired fasting glucose. This clustering was accompanied by the highest concentration of LDL-C. In our study we also noticed that the strongest predictors of mortality were hypertriglyceridemia, arterial hypertension and impaired fasting glucose. Also Dekker et al. [27] ascertained that the highest rate of mortality from cardiovascular causes (Hazard Ratios) in the group of men was demonstrated in the subgroup of patients with arterial hypertension (3.07), then with IFG (2.18) and lower HDL-C (2.17) and higher TG (0.99). The highest rate of mortality from cardiovascular causes in women was 2.27 in the subgroup of patients with higher TG and lower HDL-C (2.06), whereas with hypertension and IFG - respectively 0.87 and 0.76. Ciccone et al. [28] also confirmed that diabetes increased the risk of developing heart disease by several-fold.

Low HDL-C levels have major vasoprotective and anti-inflammatory effects, while low concentrations of HDL-C have been associated with the development of atherosclerosis, CVD, and decreased life expectancy [29]. Qahtani et al. [30] concluded that decreased levels of HDL-C were associated with increased risk of cardiovascular morbidity and mortality [31,32]. In current study we ascertained that the weakest factors of Cardiovascular morbidity were decreased level of HDL-C and also type 2 diabetes. In the Botnia Study [33] which was a large family study of subjects with type 2 diabetes and their relatives in western Finland, the presence of the metabolic syndrome was associated with a 6-fold increase in CVD mortality during the 6.9-year follow-up [34]. In persons with MetS who do not have diabetes, increased risks of CVD and CHD mortality remain.

In the literature also the relation between high blood pressure and triglyceride levels and HDL-C has been proven [35]. It was also assessed that women with metabolic syndrome including type 2 diabetes more often suffer from dyslipidemia in the form of low HDL and abdominal obesity, while in a comparable group of men hypertension occurs more often [35,36]. In our analysis we have shown that hypertension is a less determining component of the incidence of *hypercholesterolemia in patients* than impaired fasting glucose or hypertriglyceridemia, but it also adversely affects the level of the examined lipid fractions.

The study proved that the components of metabolic syndrome, especially abdominal obesity, hypertriglyceridemia, and impaired fasting glucose have a major impact on the level of LDL and non-HDL-C, which is associated with a higher cardiovascular risk. Most likely lipid-lowering drugs, statins, are given earlier to the patients diagnosed

with diabetes or hypertension, thus the incidence of cardiovascular diseases and mortality are lower than in the subgroups with IFG and hypertriglyceridemia, which was confirmed in our study.

However the study had some limitations. The cause of death and time of deaths were obtained by contacting the family via telephone, therefore it may not be accurate. Dietary information was not considered, although it is well known that saturated fat and trans fat and “neutraceuticals” products [37] are known to affect TC levels. Further studies with more power, perhaps taking into consideration the points mentioned above and with a longer follow-up period are needed to better examine the association between lipids disorders and ischemic heart mortality.

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