Original Article

ASSOCIATION OF INCREASED TRIGLYCERIDE LEVELS IN METABOLIC SYNDROME WITH CORONARY ARTERY DISEASE

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ABSTRACT

Objective: We tried to understand significance of increased triglyceride (TG) values in metabolic syndrome and coronary artery disease (CAD).

Methodology: Check up cases with a TG value lower than 60 mg/dL were collected into the first, between 60 and 99 mg/dL into the second, between 100 and 149 mg/dL into the third, between 150 and 199 into the fourth, and 200 mg/dL and greater into the fifth groups.

Results: Study included 478 cases. Values of the mean age, weight, body mass index, TG, and low density lipoprotein cholesterol (LDL-C) and prevalences of smoking, white coat hypertension (WCH), hypertension (HT), type 2 diabetes mellitus (DM), and CAD increased gradually and significantly nearly in all steps from the first towards the fifth groups.

Conclusion: Metabolic syndrome may be a progression step between complete physical health and irreversible end points, such as obesity, type 2 DM, HT, CAD, and stroke. Hypertriglyceridemia and White Coat Hypertension (WCH) may be the most significant reversible parameters of the syndrome, and it is better to have the lowest TG value as much as possible. The most significant increase was seen after the value of 100 mg/dL. The overweight, smoking, hypertriglyceridemia, hyperbetalipoproteinemia, and WCH may only be one of hundreds of parameters of the syndrome. Therefore, it is advisable that underlying etiologies rather than revesible parameters of the syndrome should be targeted for treatment. For example, increased TG and LDL-C values, and prevalence of WCH by aging may be secondary to decreased physical and mental stresses in elderly.

KEY WORDS: Triglyceride, White coat hypertension, Metabolic syndrome.

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INTRODUCTION

Close relationships between certain metabolic parameters and hypertension (HT), type 2 diabetes mellitus (DM), coronary artery disease (CAD), stroke, and eventually an increased all-cause mortality is known for many years and defined as metabolic syndrome.[1,2] Metabolic syndrome is characterized by a group of metabolic risk factors, including overweight, hyperbetalipoproteinemia, hypertriglyceridemia, white coat hypertension (WCH), insulin resistance, and a prothrombotic and proinflammatory state[3], instead of being a

certain disease since it can be reversed completely with appropriate nonpharmaceutical approaches including lifestyle changes, diet, and exercise.[4] So it actually contains the risk factors for development of irreversible end points which decrease duration and quality of life such as obesity, HT, DM, CAD, and stroke. On the other hand, although its normal limits could not been determined clearly yet, hypertriglyceridemia is one of the most significant components of the metabolic syndrome. There is an increasing evidence of a strong association between increased TG values and prevalence of CAD. Adult Treatment Panel (ATP) III adopts lower cutpoints for TG abnormalities than did ATP II.[5,6] Although ATP II determined the normal TG value as lower than 200 mg/dL, World Health Organisation (WHO) in 1999[7] and ATP III in 2001 reduced this normal limit as lower than 150 mg/dL.[5] Although these cutpoints are usually used to define limits of metabolic syndrome, there are suspicions about the safest limits of TG value in the medical literature. We tried to understand significance of higher TG values in metabolic syndrome and CAD in the study.

METHODOLOGY

The study was performed in the Internal Medicine Polyclinic of the Medical Faculty of the Dumlupinar University, on routine check up patients between August 2005 and March 2007. Consecutive patients between the ages of 15 and 70 years were studied to prevent debility induced weight loss in elders. Their medical histories including HT, DM, dyslipidemia, and already used medications were noted, and a routine check up procedure including an electrocardiography, fasting plasma glucose (FPG), TG, and low density lipoprotein cholesterol (LDL-C) was performed.

Current daily smokers, at least with six pack-months, and cases with a history of five pack-years were accepted as smokers. Patients with devastating illnesses including Type-1 DM, malignancies, acute or chronic renal failure, chronic liver diseases, hyper- or hypothyroidism, and heart failure were excluded to avoid their possible effects on weight. Additionally, anti-hyperlipidemic drugs or metformin users were also excluded to avoid their possible effects on blood lipid profile.[8]

Body mass index (BMI) of each case was calculated by same physician instead of verbal expressions. Weight in kilograms was divided by height in meters squared.[5] Cases with an overnight FPG level of 126 mg/dL or greater on two occasions or already receiving antidiabetic medications were defined as diabetics.[5] An oral glucose tolerance test with 75-gram glucose was performed in cases with a FPG level between 110 and 126 mg/dL, and diagnosis of cases with a 2-hour plasma glucose level of 200 mg/dL or greater was DM.[5] Additionally, office blood pressure (OBP) was checked after a 5-minute of rest in seated position with a mercury sphygmomanometer on three visits, and no smoking was permitted during the previous 2-hour. A 10-day twice daily measurement of blood pressure at home (HBP) was obtained in all cases, even in normotensives in the office due to the risk of masked HT after a 10-minute education about proper BP measurement techniques.[9] An additional 24-hour ambulatory blood pressure monitoring (ABP) was obtained just in cases with a higher OBP and/or HBP measurement. It was performed with oscillometrical equipment (SpaceLabs 90207, Redmond, Washington, USA) set to take a reading every 10-minute throughout the 24-hour. Eventually, HT was defined as a blood pressure (BP) of 135/85 mmHg or greater on mean daytime (between 10 AM to 8 PM) ABP, WCH as an OBP of 140/90 mmHg or greater but mean daytime ABP of <135/85 mmHg.[9] A stress electrocardiography was performed just in suspected cases as a result of the routine electrocardiography, and a coronary angiography was obtained just for the stress electrocardiography positive cases.

Eventually, patients with a TG value lower than 60 mg/dL were included into the first group. Cases with a TG value between 60 and 99 mg/dL, between 100 and 149 mg/dL, between 150 and 199, and TG value equal to or greater than 200 mg/dL were included into the

second, third, fourth, and fifth groups, respectively. The female ratio, values of the mean age, weight, BMI, TG, and LDL-C, and prevalences of smoking, WCH, HT, DM, and CAD were detected in each group and compared in between. Mann-Whitney U test, Independent-Samples T test, and comparison of proportions were used as the methods of statistical analyses.

RESULTS

The study included 478 cases (288 females), totally (Table-I). The mean ages of the groups increased up to the TG value of 200 mg/dL, significantly ($p<0.05$ in all steps), then decreased nonsignificantly (50.5 versus 48.6 years, $p>0.05$). There were 117 smokers, and only 27.3% (32) of them were females. On the other hand, prevalence of smoking was the highest in the highest TG value having cases.

The mean body weight increased continuously, parallel to the increasing value of TG, whereas BMI increased up to the TG value of 200 mg/dL, and then decreased. Similarly, the mean LDL-C reached its highest value in the fourth, and decreased significantly in the fifth groups (142.0 versus 128.5 mg/dL, $p= 0.008$). Similarly prevalence of WCH was the highest in the fourth, and decreased significantly in the fifth groups (48.2% versus 32.5%, $p<0.01$) (Table-II). As the most surprising result, prevalences of HT, type 2 DM, and CAD, as the irreversible end points of the metabolic syndrome, showed their most significant increases after the TG value of 100 mg/dL.

DISCUSSION

Although there is not any universally accepted definition for the metabolic syndrome, it basically includes five features: obesity, high glucose and insulin, low high density lipoprotein cholesterol (HDL-C), high TG, and high BP values.[10] But the already used definitions as a BP of 135/85 or 140/90 mmHg or above and a FPG of 100 or 110 mg/dL or above also include patients with DM and HT. Actually the syndrome is a collection of risk factors instead of the final diseases, and it is a reversible condition with appropriate nonpharmaceutical approaches. Whereas the diseases including HT, DM, and symptomatic atherosclerosis are irreversible and final stages which almost always require drug therapy to delay complications. For example, prevalences of hyperbetalipoproteinemia, hypertriglyceridemia, dyslipidemia, impaired glucose tolerance (IGT), and WCH showed a parallel increase to assess weight by increasing until the seventh decade and decreasing afterwards in a previous study.[11] On the other hand, prevalences of HT, type 2 DM, and CAD always continued to increase with age without any

Table-I: Characteristics of the study cases.

Variable	*TG* lower than 60 mg/dL*	*p-value*	*TG between 60 and 99 mg/dL*	*p-value*	*TG between 100 and 149 mg/dL*	*p-value*	*TG between 150 and 199 mg/dL*	*p-value*	*TG equal to or greater than 200 mg/dL*
Number	58		122		125		87		86
Mean age	33.9 ± 14.2	*0.019*	38.8 ± 13.8	*0.001*	44.8 ± 12.9	*0.002*	50.5 ± 11.2	ns	48.6 ± 10.9
Female ratio	72.4% (42)	ns†	65.5% (80)	ns	60.8% (76)	ns	56.3% (49)	ns	47.6% (41)
Prevalence of smoking	12.0% (7)	ns	14.7% (18)	*0.01*	23.2% (29)	ns	26.4% (23)	*<0.001*	46.5% (40)
Mean weight	64.9 ± 13.7	*0.000*	74.0 ± 15.6	*0.017*	78.5 ± 13.7	ns	79.6 ± 12.0	ns	80.3 ± 14.5
Mean BMI‡	24.4 ± 5.5	*0.003*	26.8 ± 6.0	*0.001*	29.3 ± 6.2	ns	29.5 ± 5.2	ns	28.8 ± 5.1
Mean TG value	51.3 ± 6.8	*0.000*	77.6 ± 10.9	*0.000*	122.2 ± 14.9	*0.000*	174.2 ± 14.7	*0.000*	263.7 ± 52.1
Mean LDL-C§ value	99.2 ± 23.1	*0.000*	116.9 ± 34.4	*0.000*	131.1 ± 30.1	*0.010*	142.0 ± 34.7	*0.008*	128.5 ± 39.1

*Triglyceride †Nonsignificant ‡Body mass index §Low density lipoprotein cholesterol

decrease indicating their irreversible properties.[11] So the metabolic syndrome is a disadvantageous but reversible status but not a final disease, and the term of metabolic syndrome probably loses most of its significance after the development of one of the irreversible end points, since from now on the nonpharmaceutical approaches will provide little benefit to prevent development of the others, probably due to cumulative effects of the risk factors on systems for a long period of time. So definition of the metabolic syndrome should be as a combination of many reversible metabolic risk factors including overweight, smoking, hypertriglyceridemia, hyperbetalipoproteinemia, and WCH for several irreversible end points, such as obesity, HT, type 2 DM, CAD, and stroke.

Probably WCH and hypertriglyceridemia are the most significant reversible parameters of the syndrome, currently[12]. Some authors have reported that WCH is associated with some features of the metabolic syndrome[13],and more than 85% of cases with the syndrome have elevated BP levels.[4] On the other hand, we observed very high prevalences of WCH even in early decades in a previous study, 33.3% in the second, 46.6% in the third, and 50.0% in the fourth decades of life.[14] The high prevalences of WCH in society were also shown in some other studies.[15-16] When we compared the sustained normotension (NT), WCH, and HT groups in another study, prevalences of nearly all of the health problems including obesity, IGT, DM, and CAD showed significant progressions from the sustained NT towards the WCH and HT groups, and the WCH group was found as a progression step in between.[17] But as an interesting finding, the prevalence of dyslipidemia was the highest in the WCH group and it was 41.6% versus 19.6% ($p<0.001$) of the sustained NT and 35.5% of the HT groups ($p<0.05$).[17] Similar results indicating the higher prevalences of dyslipidemia in WCH cases were also observed in a previous study[18], Another study showed that serum TG and cholesterol levels did not differ significantly between sustained NT, WCH, and sustained HT cases in men in the literature.[19] So the detected higher prevalences of WCH even in early decades, despite the lower prevalences of excess weight in these age groups, may show a trend of getting weight and many irreversible end points. So WCH and hypertriglyceridemia are probably two of the most significant reversible parameters rather than irreversible end points of the syndrome, thus their underlying etiologies rather than themselves should be mainly targeted for treatment.

Although ATP II determined the normal TG value as lower than 200 mg/dL[6], WHO in 1999[7] and ATP III in 2001[5] reduced this normal limit as lower than 150 mg/dL. Although these cutpoints are usually used to define limits of the metabolic syndrome, whether or not more lower limits provide additional benefits for human being is unclear. Surprisingly, we observed in the study that even a TG value of smaller than

Table-II: Associated diseases of the study cases.

Variable	*TG* lower than 60 mg/dL*	*p-value*	*TG between 60 and 99 mg/dL*	*p-value*	*TG between 100 and 149 mg/dL*	*p-value*	*TG between 150 and 199 mg/dL*	*p-value*	*TG 200 mg/dL or higher*
Prevalence of WCH†	20.6% (12)	*<0.05*	27.8% (34)	*<0.01*	40.8% (51)	ns‡	48.2% (42)	*<0.01*	32.5% (28)
Prevalence of hypertension	8.6%(5)	ns	9.0%(11)	*<0.05*	14.4% (18)	ns	12.6% (11)	ns	19.7% (17)
Prevalence of DM§	1.7%(1)	*<0.001*	6.5%(8)	*<0.001*	15.2% (19)	ns	14.9% (13)	ns	22.0% (19)
Prevalence of *CAD*Q%	1.7%(1)	ns	1.6%(2)	*<0.001*	6.4%(8)	ns	4.5% (4)	ns	4.6% (4)

60 mg/dL is better according to the reversible parameters and irreversible end points of the metabolic syndrome. On the other hand, although there were progressive increase in parameters and irreversible end points of the syndrome parallel to the increased TG value, the most significant increases were seen after the TG value of 100 mg/dL. As such we believe significantly increased mean age by the increased values of TG may be secondary to aging induced decreased physical and mental stresses, which eventually terminates with onset of reversible parameters and irreversible end points of the syndrome. Interestingly, although the mean age increased from the lowest TG having group towards the TG value of 200 mg/dL, then decreased. The similar trend was also seen in the mean LDL-C and BMI values, and prevalence of WCH. These trends may be due to the fact that although the borderline high TG values (150-199 mg/dL) is seen together with overweight, obesity, physical inactivity, cigarette smoking, and alcohol intake like acquired causes, the high TG (200-499 mg/dL) and very high TG values (500 mg/dL and higher) are usually secondary to both acquired and secondary causes such as type 2 DM, chronic renal failure, and genetic patterns.[5] Although the underlying causes of the high and very high TG values are a little bit different, probably risks of the irreversible end points of the metabolic syndrome do not change in these groups. For example, prevalences of HT and type 2 DM were the highest in the highest TG value having group in the present study. Although some authors have reported that lipid assessment in vascular disease can be simplified by measurement of either total and HDL-C levels without the need of TG[20], some others indicated a causal association between TG-mediated pathways and CAD.[21] Similarly, another study indicated moderate and highly significant associations between TG values and CAD in Western populations.[22] The present study is also significant in this regard due to being a sample of Eastern population.

In conclusion, metabolic syndrome may be a progression step between complete physical health and irreversible end points, such as obesity, type 2 DM, HT, CAD, and stroke. Hypertriglyceridemia and WCH may be the most significant reversible parameters of the syndrome, and it is better to have the lowest TG value as much as possible, but the most significant increases were seen after the value of 100 mg/dL. The overweight, smoking, hypertriglyceridemia, hyperbetalipoproteinemia, and WCH may only be one of hundreds of parameters of the syndrome. Therefore, it is advisable that underlying etiologies rather than revesible parameters of the syndrome should be mainly targeted for treament. For example, increased TG and LDL-C values, and prevalence of WCH by aging may be secondary to decreased physical and mental stresses in elderly.

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