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# The Effect of Cardiovascular Risk Factors on Metabolic Syndrome and Risk of Cardiovascular Diseases

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**Abstract**

Extensive research is focused on the study of fundamental risk factors for triggering metabolic syndrome and risk of CVD. The aim of the study is to examine whether the effect of certain cardiovascular risk factors: allostatic stress load, autonomic cardiovascular control, triglycerides, HDL-Cholesterol, arterial hypertension might induce metabolic syndrome and risk of CVD in normal weight and overweight. The cardiovascular control, assessed with heart rate variability, systolic and diastolic blood pressure (BP), and metabolic function, assessed with serum lipids, were examined in 33 physicians with normal weight and 31 physicians with overweight. Overweight was associated with significant increase in mean values of PT, PS, systolic BP, and significant decrease in mean values of $P_{THM}$, $P_{RSA}$ compared to normal weight. Overweight was associated also with significant increase in mean values of TG, TC/HDL-C, and significant decrease in mean values of HDL-C compared to normal weight. Results of our study demonstrated that the effect of constellation of cardiovascular risk factors: allostatic stress load, autonomic cardiovascular control, triglycerides, HDL-Cholesterol, arterial hypertension induces metabolic syndrome and risk of CVD in physicians with overweight. Our data show that there is a strong multiplicative and synergistic interaction between cardiovascular risk factors that enhances the onset of the metabolic syndrome and the risk of CVD. We have identified a risk of metabolic syndrome in physicians with overweight, but the situation is also disturbing and requires treatment and serious monitoring for physicians with normal weight, as we have observed a pattern of elevated TC, LDL-C, TC/HDL-C levels.

**Keywords:** Metabolic Syndrome; Cardiovascular Risk Factors; Risk of Cvd; Heart Rate Variability; Physicians; Normal Weight; Overweight

## Introduction

The fundamental risk factors for metabolic syndrome and risk for Cardiovascular Diseases (CVD) are hypertension, diabetes, smoking, high blood lipid levels, low physical activity, unhealthy eating patterns, overweight or obesity, a family history for predisposition of CVD and the new dimension of stress - allostatic stress load. The cumulative effect of allostatic stress load at work is one of the risk factors in the genesis of CVD and metabolic syndrome. Stress affects both cardiovascular function, and metabolic lipid status. Markers of high allostatic load as indices of autonomic cardiovascular control and metabolic risk are involved in the process of adaptation under chronic stress exposure. In the process of adaptation to allostatic stress load, significant physiological and pathophysiological responses and mechanisms are induced and accelerated.

For the diagnosis of metabolic syndrome, at least 3 of the following 5 factors are sufficient: abdominal obesity, increased tri glyceride levels, decreased High Density Lipoprotein-Cholesterol (HDL-C), elevated blood pressure, and elevated plasma glucose fasting. In the absence of cardiovascular disease or diabetes, the metabolic syndrome is usually their precursor. After their occurrence, the metabolic syndrome is often present, and the number of its components contributes to the risk and progression of these diseases. In our study, we will clarify the key role of triglycerides (TG), HDL-C, arterial hypertension, allostatic stress, abnormal cardiovascular control, and overweight in initiating metabolic syndrome. Our study on diagnosis of metabolic syndrome is consistent with the criteria of the National Cholesterol Education Program Adult Treatment Panel III (ATP III), which indicates the following three criteria: Serum TG> 1.7 mmol/l, HDL-C <1.0 mmol/l in men, arterial hypertension ≥ 135/85 mmHg [1].

In healthy populations reduced heart rate variability (HRV) has been shown to be a risk factor for CVD. Hypertension rarely occurs in isolation, and often clusters with other cardiovascular (CV) risk factors such as dyslipidemia and glucose intolerance [2]. This metabolic risk factor clustering has a multiplicative effect on CV risk. Overweight is a risk factor in a number of chronic

non-communicable diseases today, diseases that are the leading causes of death in much of the world, including in our country. Android-type obesity is more dangerous and correlates with dyslipidemia [high Triglycerides and Low Density Lipoprotein-Cholesterol (LDL-C), and low HDL-C], high blood glucose and high insulin resistance levels (pre-diabetes or type 2 diabetes), atherosclerosis, arterial hypertension - components of the metabolic syndrome. Elevated serum Total Cholesterol (TC) and LDL-C are factors contributing to the development of CVD. Long-term stress activation, defined from McEwen as 'allostatic load' might cause metabolic and cardiovascular syndromes inherent for CVD, type 2 diabetes and obesity [3]. Patients with hypertension, and type 2 diabetes or metabolic syndrome, often have atherogenic dyslipidemia characterized by elevated triglycerides and LDL-C, and low HDL-C [4].

The aim of the present study is to examine whether the effect of certain cardiovascular risk factors: allostatic stress load, autonomic cardiovascular control, triglycerides, HDL-C, and arterial hypertension might induce metabolic syndrome and risk of CVD in normal weight and overweight.

## Materials and Methods

Two groups of subjects participated in the study: physicians with normal weight and overweight according to the values of Body Mass Index (BMI). Normal values for BMI are between 18.5 - 24.9 kg/m2. For overweight we talk about BMI from 25.0 to 29.9 kg/m2. The first sub-group: normal weight consisted of 33 male physicians whose ages ranged from 27 to 52 years (mean age, X±SD, 42.17±10.09 yr). The second sub-group: overweight consisted of 31 male physicians, who were matched for age (mean age, X±SD, 42.12±:9.12 yr) to the first sub-group. The research study including human experimentation was done in accordance with the institutional review body of Medical University Sofia and carried out with the ethical standards of the Ethics Committee of Scientific Research at the Medical University, Sofia.

### Autonomic cardiovascular control is studied with HRV

A computerized diagnostic system for the study of autonomic cardiovascular function was applied [5,6]. HRV data were determined from ten minutes of ECG recordings between 9 a.m. and 11 a.m. in supine position after a one-hour rest period.

Following indices were analyzed:

**Time-Domain HRV Measure:**

i. X (mean RR interval) (milliseconds), resp. mean heart rate (beats per minute);

ii. Short-Term Variability (STV) (msec) (reflecting respiratory oscillations in heart rate variations) (parasympathetically mediated).

**Frequency-domain HRV measures:**

i. Spectral power of RR intervals in the Temperature band (0.01-0.05 Hz) (PT) (sympathetically mediated) (milliseconds2);

ii. Spectral power of RR intervals in the Traube-Hering-Mayer band (0.06-0.14 Hz) (PTHM) (sympathetically and parasympathetically mediated) (milliseconds2);

iii. Spectral power of RR intervals in the Respiratory Sinus Arrhythmia band (RSA) (0.15-0.50 Hz) (PRSA) (parasympathetically mediated) (milliseconds2). Spectral powers of RR intervals in the respective frequency bands were calculated using Fast Fourier Transform.

**HRV-Derived Indices:**

i. Physical Stress (PS) (mathematical algorithm based on difference between measured and age-referent values derived from the time-domain HRV measures) (arb. un.);

ii. Mental Stress (MS) (mathematical algorithm based on difference between measured and age-referent values derived from the frequency-domain HRV measures) (arb. un.);

iii. Functional Age (FA) (mathematical algorithm computing difference between measured and age-referent values of autonomic activity derived from the frequency-domain HRV measures) (years);

iv. Health Risk (HR) (%) (mathematical algorithm derived from PS, MS-coefficients and number of premature heart beats) (%).

To examine whether different mechanisms might regulate the cardiovascular function, the autonomic control was differentiated on the basis of HR values: referent – HR ≤ 25%; pre-abnormal – HR ≥ 25% - ≤ 65%; and abnormal – HR ≥ 65%. Pre-abnormal and abnormal are defined as dysfunctional control.

### Arterial Blood Pressure

Systolic and diastolic blood pressure (BP) was measured by sphygmomanometer – "Riester", No. 1360-107, Jungingen, Germany. Systolic and diastolic BP values were considered with the European Guidelines for Hypertension [2].

### Serum Lipids

Total Cholesterol (TC) (nmol/l) - investigated by an enzymatic colorimetric method using Roche apparatuses; LDL-Cholesterol (LDL-C) (nmol/l) investigated by Roche's homogeneous enzyme colorimetric method; HDL-Cholesterol (HDL-C) (nmol/l) investigated by Roche's homogeneous enzyme colorimetric method; Triglycerides (TG) (nmol/l) investigated by an enzymatic colorimetric method using Roche apparatuses; TC/HDL-C ratio.

### Data Analysis

Heart rate, HRV variables, systolic and diastolic BP, and serum lipids in sub-groups with normal weight and overweight are expressed as means±standard deviations. Means of heart rate, HRV variables, systolic and diastolic BP, and serum lipids between both sub-groups were compared by independent sample t-test. A p value < 0.05 was considered statistically significant.



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## Results

To examine differences in cardiovascular autonomic control pattern and underlying regulating mechanisms (examined with HRV), arterial blood pressure, and serum lipid profile between normal weight and overweight HRV indices, heart rate, systolic and diastolic BP, TC, LDL-C, HDL-C, TG, and TC/HDL-C were compared between each condition by independent t-test. The mean values of heart rate, HRV variables, systolic and diastolic BP, and serum lipids in physicians with normal weight and overweight are presented in Table 1. Overweight was associated with significant increase in mean values of $P_T$, PS and systolic BP, and significant decrease in mean values of $P_{THM}$, and $P_{RSA}$ compared to normal weight. When comparing both sub-groups the mean values of TC and LDL-C is not significant. However, the mean values of TC and LDL-C in both sub-groups are above the reference values (respectively 5.2 nmol/l and 2.59 nmol/l). Overweight was associated with significant increase in mean values of TG and TC/HDL-C ratio, and significant decrease in mean values of HDL-C compared to normal weight. The value of TC/HDL-C ratio was risky in both groups.

**Table 1:** Means (X±SD) and P values of functional indices in normal weight and overweight sub-groups.

| Variables | Normal Weigh t 1 (n=33) Mean (SD) | Overweight 2 (n=31) Mean (SD) | P-value 1-2 |
|---|---|---|---|
| Heart rate (beats per minute) | i68.92±9.78 | 71.92±12.28 | n.s. |
| Mean RR interval | 878.33±140.6 | 847.09±127.43 | n.s. (milliseconds) |
| STV (milliseconds) | 43.83±16.71 | 35.26±16.03 | n.s. |
| PT (milliseconds2) | 7.34±3.12 | 9.15±3.15 | .05 |
| $P_{THM}$ (milliseconds2) | 15.17±5.06 | 10.8±5.42 | .01 |
| PRSA (milliseconds2) | 14.93±4.73 | 7.93±4.15 | .01 |
| PS (arb. un.) | -.27±.06 | 2.1±.14 | .01 |
| MS (arb. un.) | -.23±.09 | .34±.11 | n.s. |
| HR (%) | 49.58±8.72 | 64.26±7.2 | n.s. |
| Systolic BP (mmHg) | 125.19±9.17 | 147.15±10.96 | 0.05 |
| Diastolic BP (mmHg) | 85.17±11.63 | 87.32±9.63 | n.s. |
| TC (nmol/l) | 6.14±1.36 | 6.1±1.45 | n.s. |
| HDL-C (nmol/l) | 1.44±.19 | 1.11±.17 | 0.01 |
| LDL-C (nmol/l) | 3.91±.39 | 4.06±.37 | n.s. |
| TG (nmol/l) | 1.41±0.38 | 4.11±1.3 | 0.05 |
| TC/HDL-C | 4.4±1.33 | 6.09±1.62 | 0.05 |

## Discussion

The results of our study revealed that the strong multiplicative and synergistic interaction between cardiovascular risk factors: allostatic stress load, overweight, autonomic cardiovascular regulation assessed by HRV, systolic and diastolic BP, and TG, HDL-C might induce metabolic syndrome in physicians with overweight. Furthermore, even with normal body weight we observed elevated levels of TC, LDL-C and TC/HDL-C that exceeded their reference values.

In our research the allostatic stress load that is typical of physicians' work as well as many other risky occupations such as those of caregivers, nurses, emergency medical technicians, air traffic controllers, fire fighters, police officers can accelerate disease processes as metabolic syndrome and risk of CVD. Allostatic stress load causes acceleration of physiological and pathophysiological mechanisms that lead to disease outcome. Early research has shown that compared to other professions physicians report having the highest workloads, greatest responsibility for others, and highest job complexity levels [7]. When physicians are subjected to stressful situations on a constant or regular basis the Hypothalamic-Pituitary-Adrenal (HPA) axis may be in a continuous elevated state of activation [8]. In our study autonomic cardiovascular control examined with HRV is affected by the level of allostatic stress load. HRV is an independent risk factor and also contributed to the increased risk for morbidity and mortality of CVD [9]. Overweight was associated with increase of sympathetic tone examined with $P_T$, $P_S$, and reduced baroreceptor modulation of heart rhythm examined with sympathetically and parasympathetically mediated $P_{THM}$ and parasympathetic tone examined with $P_{RSA}$.

The dysfunctional autonomic cardiovascular control observed in our study has been considered as one of the significant pathophysiological mechanisms of metabolic syndrome. Increased value of PS observed in our study is an indicator of reduced motor activity and physical immobilization, which are considered in cardiovascular research as modifiable, preventable cardiovascular risk factor. Our study revealed also increased value of systolic


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BP in overweight that corresponds to the Grade 1 hypertension according to the European Guidelines for Hypertension [2]. Allostatic stress load is associated with hypertension that partly mediates the greater risk of metabolic syndrome and CVD. Because hypertension is a potent risk factor for CVD it is plausible that the association between psychological distress and CVD is partly mediated through this risk factor [10]. Activation of Sympathetic Nervous System (SNS) has been considered as pathophysiological link: between cardiovascular risk factors; between high BP and metabolic syndrome; in influencing plasma lipid levels [11].

Overweight was associated with increase of TG and TC/HDL-C ratio, and decrease in HDL-C compared to normal weight. Although not statistically significant, the TC and LDL-C values are increased in both sub-groups and are above the reference values. Many recent reports confirm that elevated serum TC, LDL-C and TG are factors contributing to the development of CVD [12]. Casual influence of LDL-C on CVD is widely accepted, and the proposed causal role of TG in CVD is gaining acceptance [13]. In accordance with these findings our study reveals the increased level of TG in physicians with overweight. Physicians with overweight are with increased levels of TG, TC/HDL-C and decreased HDL-C which are significant contributing atherogenic factors to the initiation of metabolic syndrome. Our results are consistent with the findings of Badea, et al. [14] and Christensen, et al. [15] who observed that dyslipidemia may be an important factor for the development of autonomic dysfunction. This study is a continuation of our previous research in this area which revealed that decreased HRV is a strong predictor for CVD and is associated with hypercholesterolemia [16]. Chronic daily allostatic stress load experienced by the physicians and the associated continuous elevated state of activation of HPA axis and SNS in our study affects cardiovascular risk mainly by acceleration of the atherosclerotic process. HPA axis and SNS activity might precipitate endothelial dysfunction which is an important early manifestation of atherosclerosis [17]. Overweight of physicians is also a contributing factor in inducing a metabolic syndrome and a risk of CVD. Obesity appears to be key determinant of the prevalence of the metabolic syndrome [18] and is characterized by a higher degree of sympathetic activation [19]. Metabolic syndrome is considered as a group of atherosclerotic risk factors that tend to cluster and increase the risk of CVD. The metabolic syndrome risk criteria contain components of hypertension, dyslipidemia, obesity that are separately associated with disturbed HRV [20] which is consistent with the results of our present study.

## Conclusion

Results of our study demonstrated that the effect of cardiovascular risk factors: allostatic stress load, autonomic cardiovascular control, triglycerides, HDL-C, and arterial hypertension induce metabolic syndrome and risk of CVD in physicians with normal weight and overweight. Metabolic syndrome observed in physicians is a constellation of risk factors that include allostatic stress load, elevated TG, low HDL-C, hypertension, dysfunctional autonomic cardiovascular control, and overweight. Our data show that there is a strong multiplicative and synergistic interaction between cardiovascular risk factors that enhances the onset of the metabolic syndrome and the risk of CVD. We have identified a risk of metabolic syndrome in physicians with overweight, but the situation is also disturbing and requires treatment and serious monitoring for physicians with normal weight, as we have observed a pattern of elevated TC, LDL-C and TC/HDL-C levels.

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