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THE INFLUENCE OF THYROID FUNCTION AND BONE TURNOVER ON LIPOPROTEIN PROFILE IN YOUNG PHYSICALLY ACTIVE MEN WITH DIFFERENT INSULIN SENSITIVITY

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AUTHORS: Kęska A.[1], Lutosławska G.[1], Czajkowska A.[2], Tkaczyk J.[1], Mazurek K.[3], Tomaszewski P.[4]

[1] Department of Biochemistry and Biology, Józef Piłsudski University of Physical Education, Warsaw, Poland
[2] Department of Physiology, Józef Piłsudski University of Physical Education, Warsaw, Poland
[3] Department of Sports Medicine, Józef Piłsudski University of Physical Education, Warsaw, Poland
[4] Department of Statistics and Computer Science, Józef Piłsudski University of Physical Education, Warsaw, Poland

Reprint request to:
Anna Kęska
Department of Biochemistry and Biology
Józef Piłsudski University of Physical Education
01-968 Warsaw 45, Box 55
Poland
phone: +48-22-834-04-31 ext. 384
email: anna.keska@awf.edu.pl

ABSTRACT: Physical activity induces changes in the endocrine system. Previous data indicated that changes in insulin secretion and the tissue response to this hormone are very important for energy metabolism. It is believed that they are accompanied by changes in lipid metabolism, but factors contributing to this process are still disputed. The aim of this study was to assess interactions among insulin sensitivity, thyroid function, a bone turnover marker and serum lipid profile in young physically active men. Eighty-seven physical education students, aged 18-23 years, participated in the study. We measured serum levels of glucose, lipids, insulin, thyroid-stimulating hormone (TSH), osteocalcin and anthropometric parameters. Insulin sensitivity was determined using homeostatic model assessment for insulin resistance (HOMA-IR). The median value of HOMA-IR (1.344) was used to divide the study population into Group A (above the median) and Group B (below the median). Men from both groups did not differ in anthropometric parameters or in daily physical activity. Triglycerides (TG), total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) levels were higher in Group A ($P<0.05$). TSH and osteocalcin levels were similar in males with different HOMA-IR. Multiple regression analysis for TSH and osteocalcin showed that in Group A these hormones had no effect on plasma lipoproteins. However, in Group B they significantly determined the variation of plasma TC and low-density lipoprotein cholesterol (LDL-C) levels (in about 28% and 29%, respectively). We concluded that TSH and osteocalcin are involved in determination of a more healthy lipid profile at a certain level of insulin sensitivity.

KEY WORDS: TSH, osteocalcin, insulin sensitivity, lipoproteins, males

INTRODUCTION

Physical activity reduces the risk of several diseases, such as obesity, diabetes and atherosclerosis, which are currently the most common causes of morbidity and mortality in many countries [28]. Reduced risk of these diseases is a consequence of exercise-induced beneficial changes in the metabolism of carbohydrates and lipids, mediated by hormones whose secretion in physically active people differs from inactive ones [28].

Most clinical studies have shown that regular physical activity optimizes glucose metabolism mainly due to repeatedly depleting fuel storage, which enhances insulin-stimulated glucose uptake into skeletal muscle. Because skeletal muscle is the largest insulin-sensitive tissue, this leads to increase of whole-body insulin sensitivity and reduces the risk of diabetes [13]. However, several data have shown that insulin sensitivity in athletes varies with sport disciplines, as well as being different from regularly trained non-athletes [19]. Thus the physical activity influence on the tissues response to insulin seems to be more complex and not fully understood.

It is well known that changes in insulin secretion and action can influence plasma lipoproteins. It has been proven that insulin resistance (IR) is related to a more atherogenic profile, e.g. low serum high-density lipoprotein cholesterol (HDL-C) and increased serum total triglycerides (TG) [9]. There are many reports which have confirmed that diabetic patients are at increased risk of dyslipidaemia [15]. But little is known about the relationship between insulin sensitivity and lipid profile in young, non-diabetic people, especially physically active ones.

An important role in regulating metabolism of glucose and lipids and thereby in energy balance is played by thyroid hormones [17]. Thyroid hormones influence carbohydrate metabolism in skeletal muscle and adipose tissue via the positive transcriptional regulation of the muscle/fat specific glucose transporter type-4 (GLUT-4), and

stimulate lipolysis. All these steps interact with insulin action [14]. A possible interplay between insulin sensitivity and thyroid status is indicated by studies which demonstrated that the prevalence of thyroid disease in patients with diabetes is significantly higher than in the general population [5]. What is more, it is considered that dyslipidaemia in diabetic patients is the result of a complex relationship between thyroid function and IR [9]. Previous data showed that also in euthyroid non diabetic adults lipid profile appears to be modified by both insulin resistance and serum thyroid-stimulating hormone (TSH). Namely, individuals with higher insulin resistance and higher serum TSH are at greatest risk of dyslipidaemia [2]. Nevertheless, despite several investigations, many aspects of insulin resistance, lipid metabolism and thyroid function are not very clear, particularly when considering the impact of physical activity. Some authors [29] reported no major effect of exercise training on serum TSH levels in professional athletes and sedentary individuals, while others confirmed decreased TSH levels in physically active ones [23]. Therefore, the influence of physical activity on thyroid function and regulation of carbohydrate and lipid metabolism by thyroid hormones still need to be explained.

Physical exercise is responsible for changes in bone turnover, both bone formation and bone resorption [20]. However, the effect of physical activity on bone metabolism is ambiguous. Many authors have confirmed that physical activity supports the bone formation process by stimulation of osteoblast functions [25]. But there are also data confirming the increased bone resorption and higher incidence of fracture rates in some male and female athletes [30].

It has been shown that in detection of bone metabolism changes in physically active subjects bone formation markers are more sensitive than bone resorption markers [16]. One of the bone formation markers is osteocalcin. Recently osteocalcin has been reported to also affect energy metabolism through participation in regulation of glucose tolerance and insulin secretion [24]. It is believed that osteocalcin may play a protective role in the pathogenesis of type 2 diabetes, not only through direct involvement in glucose homeostasis, but also through improving the lipid profile [27].

Therefore, we have investigated interactions among insulin sensitivity using homeostatic model assessment for insulin resistance (HOMA-IR), thyroid function, a bone turnover marker and serum lipid profile in young physically active men.

MATERIALS AND METHODS

Subjects. Eighty-seven male volunteers, aged 18-23 years, were included in the study. They were physical education students, but not participating in athletic competition. Subjects were in good health, nonsmoking, on no medication. Participants were recruited by advertisements in student dormitories and by word of mouth. All men gave informed consent after receiving oral and written information concerning the study. The Ethics Commission in the University of Physical Education in Warsaw approved the study protocol.

Physical activity and body composition analysis

Activity energy expenditure (AEE) was evaluated on the basis of the Seven-Day Physical Activity Recall (SDPAR) questionnaire [26]. Body composition was estimated using the bioelectrical impedance method and BC 418 MA equipment (Tanita Co., Japan). Inter- and intra-assay coefficients of variation for body fat measurements did not exceed 5%.

Biochemical analysis

Blood samples were drawn from the antecubital vein between 7:30 and 9:00 a.m. in fasting conditions. Blood samples were collected into lithium heparin tubes using disposable syringes and needles. The samples were centrifuged (15 min, 4000 rpm, 4°C) and the plasma was stored at -70°C for subsequent analysis. The plasma concentrations of glucose were determined by the oxidase method. Plasma triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were measured with colorimetric methods. All determinations were performed using Randox commercial kits (Randox Laboratories, UK). Inter- and intra-assay coefficients of variation for glucose, TG, TC and HDL-C determination did not exceed 5%. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation [11].

Plasma levels of insulin, osteocalcin and TSH were determined by standard radioimmunoassay methods using BioSource commercial kits (Belgium). Inter- and intra-assay coefficients of variation for hormones did not exceed 7%. Sensitivity of methods was as follows: 1 $\mu IU \cdot ml^{-1}$ for insulin, 0.15 $ng \cdot ml^{-1}$ for osteocalcin and 0.025 $\mu IU \cdot ml^{-1}$ for TSH.

Insulin resistance was calculated by HOMA-IR and calculated from fasting insulin and glucose concentration according to the formula: insulin ($\mu IU \cdot ml^{-1}$) x glucose ($mmol \cdot L^{-1}$)/22.5 [21]. The median value of HOMA-IR (1.344) was used to divide the study population into Group A (above the median, n=43) and Group B (below the median, n=44).

Statistics

The data are presented as means ± SD. Normality was assessed by the Shapiro-Wilk test. The independent sample t-test or the Mann-Whitney U test was used for comparison between groups, for normally and not normally distributed variables, respectively. Logarithmic (ln) transformation was applied to right-skewed data before correlations analysis. Multiple linear regression analysis was performed to identify relationships between serum lipid parameters and TSH and osteocalcin levels. Statistical analyses were conducted using Statistica v.9 software (StatSoft, USA). The level of significance was set at alpha = 0.05.

RESULTS

As shown in Table 1, men from Group A did not differ significantly from men in Group B in BMI, body fat content and also in daily physical activity expressed in $kcal \cdot day^{-1}$.

The biochemical characteristics for men with different HOMA-IR values are listed in Table 2. Fasting plasma glucose and insulin levels were higher in Group A in comparison to Group B respectively by 11.8% ($P<0.001$) and 39.3% ($P<0.001$). Moreover, plasma TG, TC and HDL-C concentrations were significantly higher in men with HOMA-IR >median (by 22.2%, $P<0.01$ and 6.4%, $P<0.05$ and 13.3%, $P<0.05$, respectively). However, plasma TSH and osteocalcin levels were similar in both groups.

Tables 3 summarizes the results of multiple regression analysis for TSH and osteocalcin as predictors of lipid profile at different levels of insulin sensitivity. In men with higher HOMA-IR (Group A) TSH and osteocalcin levels had no effect on plasma lipoproteins. However, in Group B both hormones significantly determined the variation of plasma TC and LDL-C levels (in about 28% and 29%, respectively). Analysis of partial correlations revealed that higher TSH and osteocalcin levels in men with HOMA-IR <median were associated with lower TC and LDL-C.

DISCUSSION

It is believed that physical activity induces adaptations in the endocrine system that are essential for the physical capacity and health. The hormonal response to exercise depends on its intensity, duration, and type, as well as on the baseline individual fitness and metabolic conditions [12]. Observation of these changes allows one to evaluate whether undertaken physical activity improves body functions or disrupts homeostasis, increasing the risk of many diseases.

The present study showed that young physically active men differed in insulin sensitivity (HOMA-IR between 0.729 and 5.232).

TABLE 1. CHARACTERISTICS OF THE SUBJECTS CATEGORIZED BY HOMA-IR MEDIAN VALUE (MEANS ± SD)

Variable	Group A (n=43) HOMA-IR >1.344	Group B (n=44) HOMA-IR ≤ 1.344
Age (yr)	19.7 ± 0.8	19.9 ± 0.8
Body mass (kg)	76.4 ± 8.4	76.4 ± 9.2
Body height (cm)	180.7 ± 6.0	180.5 ± 6.1
BMI	23.5 ± 2.3	23.5 ± 2.6
Fat (%)	13.3 ± 4.6	11.9 ± 4.2
Fat (kg)	10.4 ± 4.3	9.3 ± 4.1
AEE (kcal · day^{-1})	751.1 ± 362.9	801.1 ± 346.6

Note: AEE – activity energy expenditure

TABLE 2. BIOCHEMICAL VARIABLES IN SUBJECTS DIFFERENTIATED BY HOMA-IR (MEANS ± SD)

Variable	Group A (n=43) HOMA-IR >1.344	Group B (n=44) HOMA-IR ≤ 1.344
Glucose (mmol · l^{-1})	5.1 ± 0.5***	4.5 ± 0.4
Insulin (μIU · ml^{-1})	8.9 ± 2.8***	5.4 ± 0.8
TG (mmol · l^{-1})	0.9 ± 0.4**	0.7 ± 0.3
TC (mmol · l^{-1})	4.7 ± 0.8*	4.4 ± 0.6
HDL-C (mmol · l^{-1})	1.5 ± 0.4*	1.3 ± 0.3
LDL-C (mmol · l^{-1})	2.7 ± 0.9	2.6 ± 0.6
TSH (μIU · ml^{-1})	2.1 ± 1.0	2.0 ±1.0
Osteocalcin (ng · ml^{-1})	34.5 ± 14.7	35.2 ± 13.9

Note: ***$P<0.001$; **$P<0.01$; *$P<0.05$ significantly different vs. Group B

TABLE 3. MULTIPLE REGRESSION ANALYSIS FOR TSH, OSTEOCALCIN AND LIPID PROFILE IN SUBJECTS WITH HOMA-IR HIGHER AND LOWER THAN MEDIAN VALUE

Dependent variable	Independent variable	R^2 Group A (n=43)	Partial correlation coefficients, Group A (n=43)	R^2 Group B (n=44)	Partial correlation coefficients, Group B (n=44)
TG (mmol · l^{-1})	TSH (μIU · ml^{-1})	0.067	0.223	0.130	-0.042
			P>0.05		P>0.05
	Osteocalcin (ng · ml^{-1})		-0.113		0.353
			P>0.05		P>0.05
TC (mmol · l^{-1})	TSH (μIU · ml^{-1})	0.012	-0.109	0.278	-0.310
			P>0.05		P<0.05
	Osteocalcin (ng · ml^{-1})		-0.009		-0.362
			P>0.05		P<0.05
HDL-C (mmol · l^{-1})	TSH (μIU · ml^{-1})	0.019	-0.117	0.057	0.012
			P>0.05		P>0.05
	Osteocalcin (ng · ml^{-1})		0.059		-0.229
			P>0.05		P>0.05
LDL-C (mmol · l^{-1})	TSH (μIU · ml^{-1})	0.012	-0.104	0.294	-0.374
			P>0.05		P<0.05
	Osteocalcin (ng · ml^{-1})		-0.042		-0.321
			P>0.05		P<0.05

This observation could be important because the level of insulin sensitivity determines the storage capacity of carbohydrate, the major fuel for most types of physical activities [3]. Chen et al. [8] also reported high variability in HOMA-IR values (0.90-2.91) among physically active subjects. They found that athletes with higher HOMA-IR were characterized by greater BMI than those with lower HOMA-IR values [8]. Other authors have also confirmed that one of the most important factors determining the HOMA-IR value in physically active subjects is weight status [3]. However, participants of the present study had similar BMI and also fat content. Besides, they were in the same age and did not differ in physical activity, which excluded the effect of these factors on the HOMA-IR. Therefore, our results suggest the impact of other factors on insulin sensitivity in young active men.

An interesting observation seems to be that in young lean men, differences in HOMA-IR are associated with changes in plasma lipids. Consistent with previous data, subjects with higher HOMA-IR values in this study displayed a more atherogenic lipid profile [22]. Therefore, in young people differences in insulin sensitivity can lead to significant metabolic disturbances, even though they are physically active.

In most other studies, lower HOMA-IR has been shown to be associated with higher TSH, which may be interpreted as a negative correlation between insulin sensitivity and thyroid hormones [7]. It is well known that the thyroid hormones triiodothyronine (T3) and thyroxine (T4) oppose the action of insulin. Higher serum TSH is connected with lower thyroid hormones and HOMA-IR, which may be interpreted as decreased T3 and T4 insulin-antagonistic effects [10].

According to recent data HOMA-IR is also inversely related to circulating osteocalcin [27]. Thus, it is suggested that a high level of this bone-derived hormone improves glucose tolerance.

However, our findings are in contrast to cited studies since osteocalcin levels were similar in subjects with different HOMA-IR values. The reason for this discrepancy is not clear, but it could not be excluded that physical activity of our participants affects circulating osteocalcin and its relationship with HOMA-IR. This assumption seems feasible since plasma levels of osteocalcin in active subjects are higher than in sedentary ones [6].

The most striking finding of the study is that in young physically active men insulin sensitivity determined the influence of TSH and osteocalcin on plasma lipoproteins. We found that in subjects with lower HOMA-IR values, TSH and osteocalcin contributed to decreased TC and LDL-C levels.

However, in men with higher HOMA-IR a positive effect of TSH and osteocalcin on lipoproteins did not occur. The observation that TSH levels within the reference range have been negatively associated with plasma lipids is consistent with other authors [1]. This associations is explained by the regulatory effect of thyroid hormones on the activity of some key enzymes of lipoprotein metabolism [18]. Thus, thyroid dysfunction has important health implications, including increased risk of dyslipidaemia and cardiovascular disorder [7]. Also an inverse relationship between plasma osteocalcin and lipid profile confirms previous reports suggesting that osteocalcin plays a part in the development of metabolic syndrome [4].

CONCLUSIONS

In conclusion, our results proved that in young active men the relationship between thyroid function and bone metabolism and their influence on lipid profile are dependent on insulin sensitivity. We confirmed that TSH and osteocalcin are involved in determination of a more healthy lipid profile at a certain level of insulin sensitivity.

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Conflict of interests: None declared.

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