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GENDER INFLUENCE ON RESTING METABOLIC RATE AND ADIPOCYTOKINES LEVELS IN NEWLY DIAGNOSED TYPE 2 DIABETIC PATIENTS WITH METABOLIC SYNDROME

Andrada Mihai [1,2]***, Cornelia Zetu*** [1]***, Simona Carniciu*** [1,2]***, Ariana Picu*** [1]***, Laura Petcu*** [1]***, Cristian Guja*** [1,2]***, Daniela Lixandru*** [2,✉]***, Constantin Ionescu-Tîrgovişte*** [1,2]

[1] National Institute of Diabetes, Nutrition and Metabolic Diseases "Prof. N.C. Paulescu", Bucharest, Romania
[2] University of Medicine and Pharmacy "Carol Davila", Bucharest, Romania

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Abstract

Background and Aims: *Resting metabolic rate (RMR) is important to estimate energy requirements. Our aim was to investigate the RMR in newly diagnosed type 2 diabetic (T2DM) patients with metabolic syndrome (MS) in relation with obesity, gender, some adipokines and insulin resistance parameters.* ***Material and Methods:*** *138 newly diagnosed T2DM adults were evaluated for anthropometric, clinical, biochemical parameters, and RMR. The group was subdivided according to body mass index and MS presence.* ***Results:*** *Determined RMR (RMRd), predicted RMR (RMRp), oxygen consumption and carbon dioxide production at rest were significantly lower for subjects with BMI<30 kg/m^2 compared to subjects with BMI≥30 kg/m^2 ($p<0.001$). RMRd positively correlated with fat-free mass ($p < 0.001$), waist ($p < 0.001$), BMI ($p < 0.001$), insulinemia ($p = 0.021$) and negatively with age ($p < 0.001$) and adiponectin ($p = 0.027$). The percent of determined from predicted RMR in subjects with MS was lower than in those without MS, but only for men ($p<0.005$).* ***Conclusions:*** *Subjects with T2DM and MS have significantly lower than predicted RMR, compared to those without MS, indicating that they may have an energy sparing metabolism. Gender influences the energy metabolism and may play a particular role in energy the metabolism of people with T2DM and MS.*

key words: *type 2 diabetes, metabolic syndrome, resting metabolic rate, obesity*

Background and Aims

Although obesity prevalence data vary with the methods chosen for evaluation, gender, race and socio-economic aspects, the epidemiological studies from the last decades showed that the prevalence of overweight and obesity has reached epidemic proportions in many parts of the world. For example, in the United States of America about one-third of the adult population is obese [1]. Increasing prevalence of obesity is accompanied by increased prevalence of obesity-related metabolic and cardiovascular comorbidities such as metabolic syndrome (MS), dyslipidemia, type 2 diabetes (T2DM), hypertension, ischemic heart disease, and stroke

✉ 8, Eroii Sanitari Blvd, 050474, Bucharest, Romania; phone: +40213180862/145
corresponding author e-mail: daniela.lixandru@umf.ro

[2]. Data released in 2011 by the International Federation of Diabetes showed that 366 million people had diabetes and that by 2030 the number will increase to 552 million [3]. Cases of T2DM represent more than 85% of cases and the highest number of people with diabetes belongs to the 40 to 59 age group [3].

Obesity is caused by a combination of genetic predisposition and environmental factors. An excessive energy intake, unbalanced with the real needs, and a sedentary lifestyle are well recognized and studied causes of obesity [4]. Apart from these well known factors, differences in energy metabolism may also play a role in predisposition to excess adiposity and may be an important factor in the etiology of obesity and its associated comorbidities like MS and T2DM. Resting metabolic rate (RMR) represents the energy needed in order to maintain the vital functions and reflects the energy consumed by the organs and skeletal muscle mass [5]. RMR represents the main component of energy requirements and accounts for 65-70% of the total energy expenditure in sedentary adults. The main method to measure the RMR is indirect calorimetry. Oxygen consumption (VO_2) and carbon dioxide production (VCO_2) are measured in order to calculate the metabolic rate. Between RMR and the mitochondrial function there is a close relationship [6]. RMR is mainly influenced by the muscle mass, but it also varies with age, gender, some genetic traits [7], fat mass, disease status, and level of circulating hormones [8]. A low RMR was indicated as a risk factor for weight gain [9,10]. In T2DM patients, there are studies that reported higher resting metabolic rates when compared with non-diabetic subjects [11-15]. There are also studies which reported that MS is characterized by a low resting metabolic rate, at least in some subjects [16-17].

The aim of our study was to investigate the RMR in newly diagnosed T2DM patients stratified according to gender, weight status or on the basis of presence or absence of MS in order to better characterize the variation of RMR in this population. We also evaluated RMR among these patients in relation to some parameters of insulin resistance and some adipokines. Our study population represents a very interesting one because at the moment of diagnosis T2DM subjects had various degree of hyperglycemia and they were not receiving any antidiabetic treatment.

Material and Methods

The study was cross-sectional, including 138 adults newly diagnosed with T2DM, from the specialized diabetes outpatient clinic of the National Institute of Diabetes, Nutrition and Metabolic Diseases (NIDNMD) "Prof. N.C. Paulescu". The subjects were referred to the diabetes clinic by their general practitioners, by other specialists or by self referral.

Inclusion criteria for the study were: age between 35 and 85 years old and a recent diagnosis of T2DM (less than 6 months). The diagnosis of diabetes mellitus was established using the American Diabetes Association (ADA) [18] and World Health Organization (WHO) definition [19,20]: plasma glucose $\geq$ 7.0mmol/l (126mg/dl), or 2–h plasma glucose on oral glucose tolerance test (OGTT) $\geq$ 11.1mmol/l (200mg/dl), or an $HbA_{1c} \geq 6.5\%$ (using a method that is NGSP (National Glycohemoglobin Standardisation Program) certified and standardized to the DCCT (Diabetes Control and Complications Trial) assay) or a random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) in patients presenting classical symptoms of hyperglycemia such as polyuria, polyphagia, polydipsia and weight loss. Subjects were not following any special medical diet or taking antidiabetic medication.

In order to establish the diagnosis of MS we used latest published consensus definition [21] according to which three or more of the following criteria must be met: (*i*) abdominal obesity: increased waist circumference (using the AHA/NHLBI recommended cut points of ≥102 cm for men and ≥88 cm for women), (*ii*) elevated triglycerides: ≥150 mg/dL or specific treatment for this lipid abnormality, (*iii*) decreased HDL-cholesterol: <40 mg/dL in men, <50 mg/dL in women, or specific treatment for this lipid abnormality, (*iv*) increased blood pressure systolic ≥130 and/or diastolic ≥85 mm Hg, or antihypertensive drug treatment in patients with history of hypertension, and (*v*) increased fasting glucose > 100 mg/dL, or drug treatment for diabetes. All of our patients had diabetes so they had one component of the syndrome.

Exclusion criteria were: type 1 diabetes, symptoms or signs of acute or chronic infection, significant pulmonary disease, malignancies, chronic liver disease, excessive alcohol consumption, epilepsy or other severe neurological diseases, chronic renal disease with an eGFR lower than 60 ml/min/1.73 m^2.

The approval of the Ethics Committee of NIDNMD "Prof. N.C. Paulescu" for the study protocol was obtained. Each participant signed an informed consent before inclusion into the study.

Data regarding lifestyle (including smoking), family history, personal medical history, and concomitant medication were noted. Weight (in light clothing) and height (barefoot) were measured using a standardized height and weight scales. Body mass index (BMI) was calculated as weight (in kilograms)/height (in $meters^2$). The waist circumference was measured with the subject standing, at mid distance between the lowest rib and the iliac crest, at the end of normal expiration. The blood pressure was determined in sitting position. Fat mass, fat-free mass and visceral fat were estimated using a resistometric evaluation (body composition analyzer MC-980 from TANITA).

Blood samples were obtained in the morning, after 8-10 hours of fasting. The concentration of fasting glucose (mg/dL), glycated hemoglobin (HbA_{1c}) (%), total cholesterol (mg/dL), high density cholesterol (HDL-chol; mg/dL), total triglycerides (mg/dL), urea (mg/dL), creatinine (mg/dL), uric acid (mg/dL) were measured using current biochemical methods (Hospitex Diagnostincs Eos Bravo Forte Analyser). Low density cholesterol (LDL-chol) was calculated using the Friedewald formula [22]. Serum concentrations of insulin, proinsulin, C peptide, leptin and adiponectin were determined by ELISA method (Multiskan Ex-Thermo Electro Corporation) using commercially available kits (EIA-2935, EIA-1560, EIA-1293, EIA-2395 and EIA-4177; DRG Instruments, Germany) following the manufacturer's guidelines. HOMA-IR (*Homeostasis Model Asessment for Insulin Resistance*) was determined as [glycemia (mmol /L) x insulinemia (μU / mL)]: 22.5 [23].

RMR was determined by indirect calorimetry, using an automated metabolic measurement system (Cosmed Quark CPET; Rome, Italy), according to manufacturer's specifications, in the same morning, also in fasting condition. Data (oxygen consumption – VO_2 and carbon dioxide production – VCO_2) were collected and analyzed over a 20 min interval, after an initial period of 10 min used for habituation only, in standardized medium conditions (temperature, humidity, noise and body position) that were maintained constant during the test. "Predicted RMR" was calculated according to the Harris Benedict equations [24]. The Weir equation was used to calculate resting metabolic rate, as follows: RMR (kcal/day) = [3.941(VO_2 (ml/min)) + 1.11(VCO_2 (ml/min))] 1.44 [25,26].

Statistical analysis was performed with Epi Info 7.1.0.6 statistical software (Centre for Disease Control, Atlanta). First we realized a descriptive analysis of the variables. The population clinical and biochemical characteristics were presented as mean ± standard deviation. Categorical variables values were compared between women and men, different categories of BMI, and between those with or without the MS by using Chi Square test**.** A p value of ≤ 0.05 was considered to indicate a significant difference. Pearson's correlation was used to establish association between the analyzed parameters.

Results

Overall the study group included 138 subjects (66 females and 72 males). The mean BMI for studied subjects was 30.97 kg/m^2, 55.8% of them being obese, most of them with BMI within 30 to 34.9 kg/m^2 range. According to BMI, the study subjects were divided into normal eight and overweight subjects (group 1), respectively obese subjects (group 2). A total of 84.8 % of studied patients fulfilled the criteria necessary for the diagnosis of metabolic syndrome, 66 being women and 72 men, most of them having 3 (35.5%) or 4 traits of MS (26.8%). After diabetes (present in all our patients), the decreasing frequency of the MS components was: increased waist circumference (82.6%), high blood pressure (73.9%), low HDL-cholesterol (57.2%), and increased levels of triglycerides (40.6%).

Table 1. Main clinical characteristics of the study subjects divided according to BMI.

	All subjects (n=138)	**Group 1 BMI <30 kg/m^2 (n=61)**	**Group 2 BMI ≥30 kg/m^2 (n=77)**	**p-value between groups**
Age (years)	59.12 ± 10.2	59.87 ± 10.23	58.52 ± 10.21	NS
Waist (cm)	105.45 ± 10.66	98.00 ± 9.31	111.35 ± 7.53	**< 0.001**
SBP (mmHg)	131.05 ± 12.60	129.43 ± 14.05	132.34 ± 11.25	NS
DBP (mmHg)	74.68 ± 7.49	72.72 ± 7.93	76.23 ± 6.79	**< 0.05**
Glycemia (mg/dL)	177. 77 ± 65.5	188.39 ± 77.51	169.35 ± 53.22	NS
HbA_{1c} (%)	7.92 ± 1.94	8.25 ± 2.35	7.65 ± 1.50	NS
Total cholesterol (mg/dL)	212.61 ± 50.33	215.71 ± 52.80	210.15 ± 48.48	NS
HDL- cholesterol (mg/dL)	44.29 ± 12.14	45.11 ± 11.92	43.65 ± 12.35	NS
Triglycerides (mg/dL)	169.42 ± 101.47	165.47 ± 110.42	172.55 ± 94.41	NS
LDL – cholesterol (mg/dL)	134.85 ± 45.54	136.98 ± 46.24	133.16 ± 45.23	NS
AST (U/mL)	22.20 ± 9.72	21.31 ± 10.13	22.89 ± 9.41	NS
ALT (U/mL)	29.27 ± 17.07	25.69 ± 15.62	32.02 ± 17.72	**< 0.05**
Uric Acid (mg/dL)	5.32 ± 1.69	4.99 ± 1.58	5.59 ± 1.74	**< 0.05**
GGT (U/mL)	40.77 ± 28.36	36.18 ± 21.94	44.40 ± 32.24	NS
Insulin (µIU/mL)	14.58 ± 11.04	11.25 ± 5.83	17.21 ± 13.30	**< 0.001**
HOMA – IR	6.73 ± 9.01	5.08 ± 3.17	8.04 ± 11.59	**< 0.05**
C-peptide (ng/dL)	4.66 ± 3.02	4.19 ± 3.39	5.04 ± 2.67	NS
Leptin (ng/mL)	17.07 ± 15.26	9.22 ± 8.33	23.28 ± 16.63	**< 0.001**
Adiponectin (µg/mL)	7.73 ± 7.61	8.05 ± 6.59	7.47 ± 8.36	NS

Results are presented as mean values ± standard deviation. NS – not significat. SBP – systolic blood pressure; DBP – diastolic blood pressure; AST – aspartat aminotransferase; ALT - alanin aminotransferase; GGT – gama glutamiltransferase.

The main anthropometric, clinical and biochemical characteristics of the study subjects (comparatively for the whole study group, normal weight/overweight and obese subjects)

are reported in Table 1 as means ± standard deviation (SD). Obese subjects had higher values for fat mass (FM, kg) (38.43 ± 7.02 vs. 31.84 ± 7.6, p < 0.001), and also for fat-free mass (FFM, kg) (52.29 ± 12.45 vs. 47.70 ± 11.17 p=0.024) than non-obese subjects. Obese subjects had higher insulin levels and were more insulin resistant than subjects in group 1.

Table 2. Resting metabolic rate and other calorimetry data in the study subjects divided according to BMI.

	All subjects (n=138)	**Group 1 BMI <30 kg/m^2 (n=61)**	**Group 2 BMI ≥30 kg/m^2 (n=77)**	**p-value between groups**
RMRd (kcal/day)	1569.34 ± 321.40	1463.66 ± 251.11	1653.06 ± 346.93	< **0.001**
RMRp (kcal/day)	1635.81 ± 273.58	1523.92 ± 228.67	1724.45 ± 275.00	< **0.001**
RMR/FFM (kcal/kg)	32.70 ± 9.76	31.90 ± 7.62	33.33 ± 11.17	NS
RMRd – RMRp	-65.80 ± 205.27	-58.75 ± 164.64	-71.39 ± 233.42	NS
VO_2 rest (ml/min)	228.08 ± 46.69	213.31 ± 36.66	239.78 ± 50.54	< **0.001**
VCO_2 rest (ml/min)	182.43 ± 39.89	168.20 ± 30.85	193.71 ± 42.72	< **0.001**
RQ	0.80 ± 0.06	0.78 ± 0.05	0.80 ± 0.07	NS

Results are presented as mean values ± standard deviation. NS – not significat.

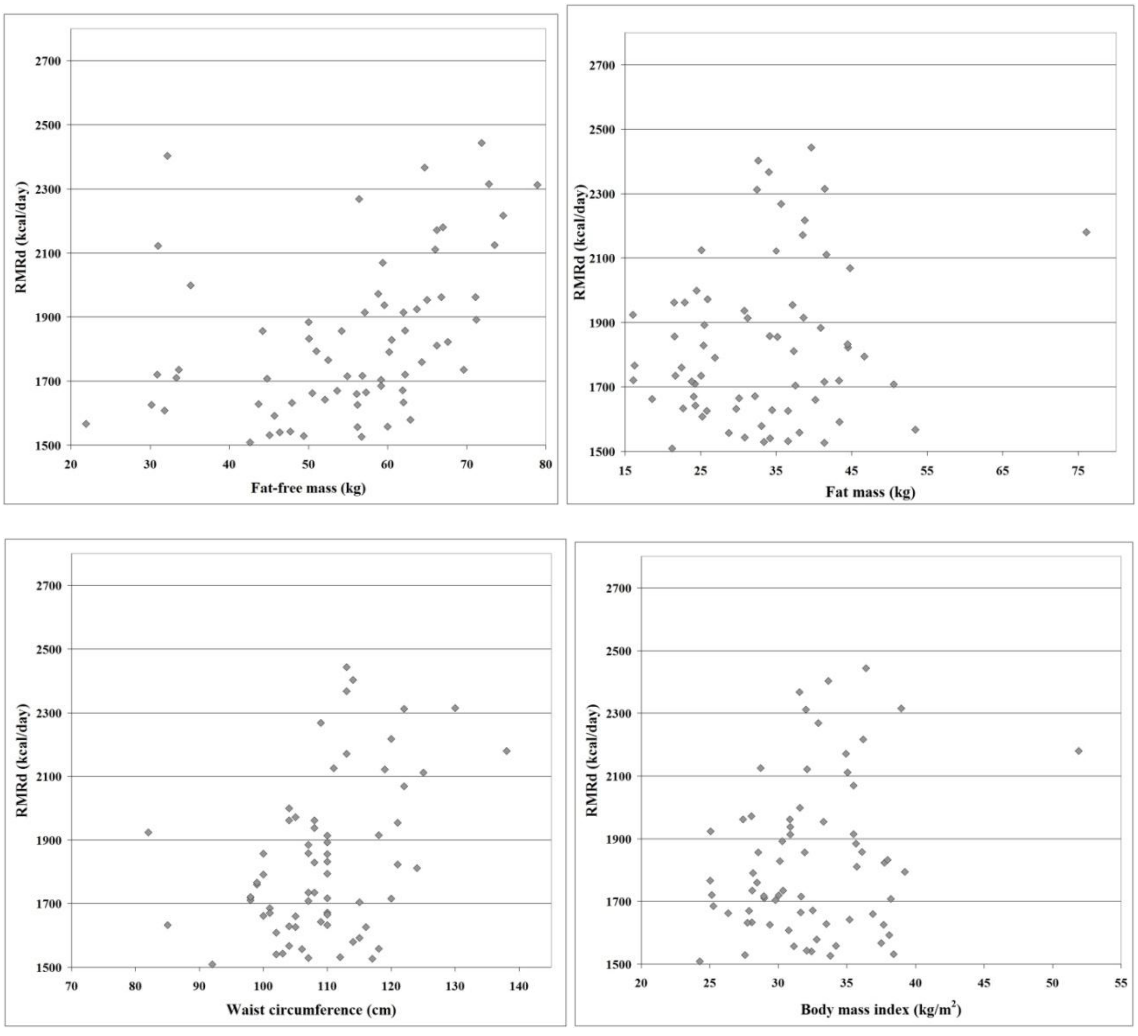

Figure 1. *Correlations between determined RMR and fat-free mass, waist circumference, body mass index and fat mass in the study group.*

Results for determined RMR (RMRd), predicted RMR (RMRp), RMR adjusted for fat-free mass (RMR/FFM), oxygen consumption (VO_2) at rest, carbon dioxide production (VCO_2)

at rest and respiratory quotient (RQ – VCO_2/VO_2) are presented in Table 2, for all subjects and for the two analyzed groups. Mean values for determined RMR were significantly lower than mean predicted RMR values for all patients ($p < 0.001$). 45.7% of the subjects had a determined RMR value lower than predicted RMR, with no significant differences between various BMI categories. Both predicted and determined RMR absolute values were statistically significant higher among obese patients than in patients with a BMI < 30 kg/m^2, but the difference was not maintained when RMR was adjusted for fat-free mass.

In newly diagnosed T2DM patients, the determined RMR correlated strongly with fat-free mass ($r = 0.516$, $p < 0.001$), waist circumference ($r = 0.455$, $p < 0.001$), BMI ($r = 0.342$, $p < 0.001$), and to a lesser degree to fat mass ($r = 0.219$, p 0.01) as shown in Figure 1.

A negative correlation of RMR was found with age ($r = -0.463$, $p < 0.001$). The oldest patients (aged 70-80 years) had the lowest RMR 1369.50 ± 213.25 kcal/day, significantly different ($p < 0.001$) from the youngest patients (aged 35-40 years) (2058.83 ± 248.74 kcal/day). Men had higher RMR than women (1724.13 ± 308.10 vs. 1400.48 ± 241.96 kcal/day; $p < 0.001$). We also noticed other statistically significant correlations between RMR and insulinemia ($r = 0.197$, p 0.021) and adiponectin ($r = -0.188$ p 0.027). No correlations were found for C-peptide, HOMA-IR or leptin.

We further analyzed our T2DM patients according to the presence or absence of MS. The differences in anthropometric, clinical and biochemical characteristics between T2DM patients with (MS+) or without (MS-) MS are presented in Table 3.

Table 3. Anthropometric, clinical and biochemical characteristic of newly diagnosed T2DM subjects according to the presence or absence of metabolic syndrome.

	All subjects (n=138)	**MS- group (n=21)**	**MS+ group (n=117)**	**p-value between groups**
Age (years)	59.12 ± 10.2	56.29 ± 9.74	59.62 ± 10.24	NS
Waist (cm)	105.45 ± 10.66	96.00 ± 11.70	107.15 ± 9.57	< **0.001**
BMI (kg/m^2)	30.98 ± 4.50	26.72 ± 2.60	31.74 ± 4.34	< **0.001**
SBP (mmHg)	131.05 ± 12.60	127.62 ± 12.20	131.67 ± 12.62	NS
DBP (mmHg)	74.68 ± 7.49	70.52 ± 9.34	75.43 ± 6.90	< **0.05**
Glycemia (mg/dL)	177. 77 ± 65.5	178.50 ± 53.92	177.63 ± 67.59	NS
HbA_{1c} (%)	7.92 ± 1.94	7.81 ± 1.70	7.93 ± 1.98	NS
Total cholesterol (mg/dL)	212.61 ± 50.33	216.76 ± 34.13	211.86 ± 52.79	NS
HDL- cholesterol (mg/dL)	44.29 ± 12.14	51.67 ± 10.19	42.97 ± 12.02	< **0.001**
Triglycerides (mg/dL)	169.42 ± 101.47	114.24 ± 74.73	179.32 ± 102.70	< **0.001**
LDL – cholesterol (mg/dL)	134.85 ± 45.54	142.23 ± 28.66	133.44 ± 48.07	NS
AST (U/mL)	22.20 ± 9.72	18.38 ± 5.50	22.90 ± 10.17	< **0.05**
ALT (U/mL)	29.27 ± 17.07	23.65 ± 15.16	30.30 ± 17.26	NS
Uric Acid (mg/dL)	5.32 ± 1.69	4.33 ± 1.27	5.50 ± 1.70	< **0.05**
GGT (U/mL)	40.77 ± 28.36	29.92 ± 13.11	42.72 ± 29.92	< **0.05**
Insulin (µIU/mL)	14.58 ± 11.04	9.30 ± 3.90	15.52 ± 11.64	< **0.001**
HOMA – IR	6.73 ± 9.01	4.05 ± 1.97	7.21 ± 9.67	< **0.05**
C-peptide (ng/dL)	4.66 ± 3.02	3.35 ±2.17	4.90 ± 3.09	< **0.05**
Leptin (ng/mL)	17.07 ± 15.26	6.21 ± 4.87	19.02 ± 15.68	< **0.001**
Adiponectin (µg/mL)	7.73 ± 7.61	7.51 ± 5.46	7.77 ± 7.95	NS

Results are presented as mean values ± standard deviation. NS – not significant.

We further analyzed the influence of gender on different traits in patients with / without MS. In men we found significant differences for the same parameters as in the whole studied group. In women the differences remained almost the same, with the exception of diastolic blood pressure which was no longer significantly different and of ALT which presented significantly higher values in MS+ patients (27.77 ± 17.81 vs. 16.87 ± 4.64; $p < 0.001$).

RMR and gases exchanges in all subjects and separately for women and men were examined according to presence or absence of MS and the results are presented in Table 4.

Table 4. Resting metabolic rate and other calorimetry data in patients with (MS+) or without (MS-) metabolic syndrome.

	All subjects (n=138)		**Women (n=66)**		**Men (n=72)**	
	MS -	**MS +**	**MS -**	**MS+**	**MS -**	**MS+**
RMRd (kcal/day)	1573.14 ± 242.68	1568.66 ± 334.42	1358.63 ± 197.44	1406.26 ± 248.38	1705.15 ± 160.81	1728.31 ± 332.79
RMRp (kcal/day)	1548.05 ± 203.20	1651.5 ±6 282.19	1364.88 ± 134.95	1449.67 ± 161.79	1660.77$^{\$}$ ± 148.52	1850.03$^{\$}$ ± 229.58
RMR/FFM (kcal/kg)	31.24 ± 3.79	32.96 ± 10.46	33.16 ± 3.77	33.82 ± 9.61	30.06 ± 3.42	32.11 ± 11.25
RMRd – RMRp	29.48* ± 140.09	-82.91* ± 210.81	-6.25 ± 119.24	-43.41 ± 193.82	51.46$^{\$}$ ± 151.79	-121.73$^{\$}$ ± 221.06
VO_2 rest (ml/min)	230.33 ± 34.98	227.68 ± 48.61	199.13 ± 28.86	204.21 ± 35.93	249.54 ± 22.46	250.75 ± 48.62
VCO_2 rest (ml/min)	178.00 ± 30.53	183.23 ± 41.41	153.00 ± 23.15	164.10 ± 32.83	193.38 ± 23.84	202.03 ± 40.55
RQ	0.77** ± 0.04	0.80** ± 0.07	0.76$^{\#}$ ± 0.03	0.80$^{\#}$ ± 0.07	0.77$^{\$\$}$ ± 0.05	0.80$^{\$\$}$ ± 0.06

Significant differences between MS-/MS+ patients *$p < 0.05$; **$p < 0.005$.
Significant differences between women MS-/MS+ $^{\#}$ $p < 0.05$.
Significant differences between men MS-/MS+ $^{\$}$ $p < 0.005$; $^{\$\$}$ $p < 0.05$.

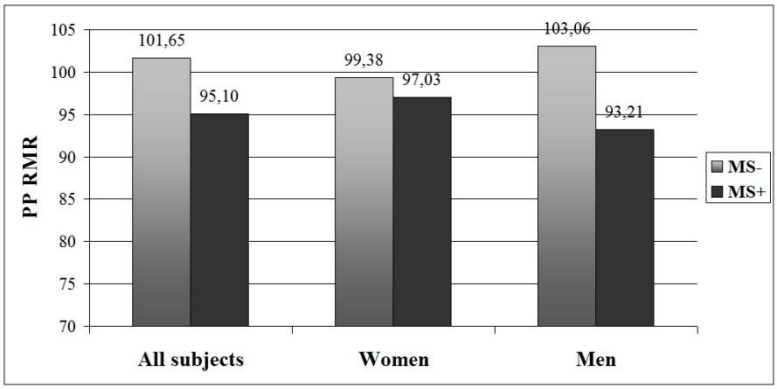

Figure 2. *The percent of determined RMR from predicted RMR (PP-RMR) in T2DM patients with or without MS.*

We calculated the percent represented by determined RMR from predicted RMR, abbreviating this parameter as PP-RMR. We found that the subjects with MS had lower PP-RMR than the subjects without the syndrome ($p < 0.005$) as shown in Figure 2. The difference was statistically significant for men ($p < 0.005$) but not for women.

Discussions

This study investigated 138 newly diagnosed T2DM subjects that were divided into subgroups according either to their body mass index (BMI < 30 vs. BMI ≥ 30 kg/m^2) or to the presence (MS+) or absence (MS-) of the metabolic syndrome. Measurement of energy expenditure by RMR is the main element to estimate the energy requirements. Insulin resistance [27],

increased gluconeogenesis [28], increased sympatethic activity [29], altered free fatty acids metabolism or stimulation of mitochondrial uncoupling proteins [12,13], and abnormal protein metabolism [30] are some possible explanations for abnormal metabolic reactions in subjects with T2DM. There are consistent results describing higher resting metabolic rates in T2DM patients [11-15] when compared with non-diabetic subjects. We therefore examined RMR in newly diagnosed T2DM patients and we found strong correlations between RMR and fat-free mass, and also for clinical anthropometric measurements like waist circumference or BMI, that can easier be determined in daily clinical practice. We established a weaker correlation with total fat mass. Age has a significant negative effect on RMR, older patients having lower RMR. This variation with age was described to be independent of any age-related changes in body composition [8]. Our results also showed that gender influences RMR, men having higher RMR than women.

Obesity is associated with insulin resistance and T2DM [31], production of proinflammatory cytokines by hypertrophic adipocytes being thought to represent the link between them [32]. We found a significant negative correlation between serum adiponectin, an antiinflammatory cytokine and RMR, as also described by others [33], and interpreted to be a mechanism of protection against obesity associated disorders. However, consistent with other reports [8,34], our study did not show a correlation between leptin, a proinflammatory cytokine, and RMR.

Our main finding in patients with T2DM and MS is a significantly lower determined than predicted RMR (analyzed or as PP-RMR), when compared with T2DM subjects without MS. This result was significant in men but not in women, supporting the idea that gender may also play a role in energy metabolism of people with T2DM and MS. Our results indicate that T2DM patients with MS may have an energy sparing metabolism, in accordance with other similar findings in obese subjects with MS [16].

Conclusions

Our results show that in newly diagnosed T2DM patients determined and predicted RMR are associated to obesity degree. Subjects with T2DM and MS have significantly lower determined than predicted RMR compared to those without MS, indicating they may have an energy sparing metabolism. Gender influences the energy metabolism and may play a particular role in the energy metabolism of people with T2DM and MS.

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