

Primary Health Care Department of Family Medicine Department
Medical University of Lublin

GRAŻYNA MARDAROWICZ, JERZY ŁOPATYŃSKI, TERESA NICER

Our research on polimetabolic syndrome

Polimetabolic syndrome is a descriptive term for a simultaneous association of some commonly occurring pathologies such as: obesity, diabetes, dyslipidaemia, arterial hypertension and others, which play a role in the development of angiopathy – a cause for mortality in contemporary societies. Awareness of the importance of this syndrome in clinical medicine has grown over the period of the last couple of decades. Wohlstandsyndrom (Mehnert, 1968), hormonal and metabolic syndrome (Bjorntrop, 1988), X syndrome (Reaven, 1988), death quartet (Kaplan, 1989), Reaven's syndrome, plurimetabolic syndrome (Crepaldi, 1993) – 5,12 – are the terms that have been used in medical literature. In the 1990's new terms started to be commonly used: „insulin resistance syndrome” and, interchangeably, „metabolic syndrome”. Gerald Reaven was the first to emphasize etiopathogenetic significance of insulin resistance in subjects with metabolic syndrome (12). Components of the described syndromes differed from each other. Tracking the history of the development of the „metabolic syndrome” term is impeded by unstable criteria of obesity, diabetes, arterial hypertension and dyslipidaemia recognition that have been changed many times over the last decades.

Basing on the fact that in type 2 diabetes one can observe sudden cardiac death without preceding cardiologic history, in 2001 I.W.Cambell and H. Purcel suggested the name *silent sextet* for metabolic syndrome. The features of “the silent sextet” are: central obesity, glucose intolerance or type 2 diabetes, arterial hypertension, dyslipidaemia (increased triglycerides, lowered HDL- cholesterol), increased blood coagulability, atherosclerosis (2).

In recent years World Health Organization introduced a working definition of the syndrome and defined quantitative criteria of its recognition, which have been commonly accepted (16). According to WHO, metabolic syndrome is an association of impaired glucose tolerance or diabetes and/or insulin resistance (defined as glucose uptake in the conditions of hyperinsulinaemia and euglicaemia in the lower quartile interval for the studied population) accompanied by at least two of the elements mentioned below: raised arterial hypertension values $\geq 140/90$ mm Hg; raised triglycerides concentration levels ≥ 1.7 mmol/l (150 mg%) and/or low HDL cholesterol level < 0.9 mmol/l (35 mg%) in men or < 1.0 mmol/l (39 mg%) in women; central obesity (waist/hip ratio WHR > 0.9 in men or > 0.85 in women and/or body mass index BMI ≥ 30 kg/m²); microalbuminuria (excretion of albumins with urine > 20 μ g/min or albumin/creatinine ratio 30 mg/g); a number of other components of metabolic syndrome have been described so far (e.g. hyperuricaemia, coagulation disorders, raised PAI-1 level and others), but their occurrence is not necessary for the diagnosis.

OUR RESEARCH ON DEVELOPMENT OF METABOLIC SYNDROME

OUR RESEARCH ON THYREOTOXIC SUBJECTS

At the end of the 1970's we started our research on behaviour during the thyreostatic treatment of various pathologies, the associations of which are presently defined as metabolic syndrome. We noticed that the body mass of subjects with thyreotoxicosis increased by 3–5% of the body mass from before the treatment already within 4 weeks (9). We also observed a significant increase of total cholesterol, mostly carried by LBL. As the thyreostatic treatment usually lasts for 1.5–2 years and the increase in body mass and hyper-LDL-cholesterolaemia are accompanied by other arteriosclerosis risk factors such as impaired glucose tolerance, frequent in patients with thyreotoxicosis (but also after its regression), as well as decreased motor activity, a proposition was submitted that the danger of accelerated development of arteriosclerosis could increase significantly during the thyreostatic treatment (8,9). It could seem that the suggestion was hasty but further observation proved that after 2 years of thyreostatic treatment body mass increased by 16% on average ($p < 0.001$) – 11. Overweight exceeding 115% of the proper body weight (calculated according the Brocic brothers formula with Brousch's correction) was found in 43.5% of the examined subjects and in as many as 84.1% after 2 years of treatment. Arterial hypertension (over 159/94 mmHg) was twice as frequent: in 13% of subjects before the treatment and in 27.5% after 2 years. Total cholesterol increase amounted to 40% and in some subjects it exceeded 100% of the base value; in 14.4% HDL-cholesterol decrease was found. According to the guidelines of the Polish Coronary Disease Prevention Programme (13), two years after the start of the thyreostatic treatment as many as 75% of the examined should be declared as endangered with high coronary disease risk and should be submitted to active prevention. These results allowed the author [G.M] to submit a proposition: subjects treated over a long period of time because of their thyreotoxicosis can be in danger of accelerated development of arteriosclerosis complications in connection with the growth of certain risks factors' levels. This refers to: hypercholesterolaemia, arterial hypertension, and obesity.

Observing over the period of 15 years a group of 300 successively coming patients with the first thyreotoxicosis diagnosis, Mardarowicz found that during that period many of them developed metabolic syndrome, much more frequently than in the control group. In patients with metabolic syndrome raised fasting insulin was found in serum concentration, which, in the opinion of the author, clearly suggests a relationship of insulin resistance and metabolic syndrome in the examined (10).

OUR EXAMINATION OF THE LUBLIN REGION VILLAGERS IN THE 1987-1989 PERIOD

In the period between 1987–1989 we started to examine the countryside inhabitants of the former Lubelskie Voivodship. Despite gradual decrease in the number of village inhabitants in Poland, they still constitute almost a half of the entire population in the Lublin Region. The aim of this study was to describe the health status of the adult population of villages in our region who worked on their farms only and thus were not subject to obligatory periodical medical examinations. In the period of 1987–1989 we examined as many as 11 546 randomly chosen people (7209 women and 4337 men) aged 18 and over in 16 gminas (communes). The examined were weighed (by means of medical scales) and measured (measuring tape). Besides a measurement of their arterial blood pressure was taken. Routine medical examinations were also carried – resting ECG was measured and fasting blood samples were taken to determine glucose, total cholesterol, and creatinine in blood serum levels. Overweight and obesity were diagnosed based on the contemporary WHO criteria: body mass index $BMI > 23.8$ – 28.5 and $BMI > 28.6$ for women respectively, and for men $BMI > 25$ – 29.9 and $BMI > 30$ respectively. We found

overweight in 36% of women and 34% of men and obesity in 30% of women and 10% of men, which was a higher rate than in the studies of populations in many European countries in those years. Prevalence of overweight and obesity increases along with the age of the examined subjects. The rate of persons with arterial hypertension (40%), hypercholesterolaemia (7.8%), glucose tolerance disorders (16%), and diabetes (13%) grows significantly in the group of obese subjects. Prevalence of hypertension in the entire studied group was found at the level of 24.2% (14.5% in the normal weight group and 32% in the overweight group), ischaemic heart disease at 20.8% (18.0% and 23% respectively), diabetes at 2.7% (1.4% and 3.7% respectively). The results of our study showed that the prevalence of obesity, arterial hypertension, and diabetes was in that period higher than we expected and higher than in other European populations (7, 8).

RESEARCH CARRIED AMONG THE INHABITANTS OF THE LUBLIN TOWN AND THE LUBLIN REGION VILLAGES IN 1998-2000

The aim of this study was to evaluate the prevalence of type 2 diabetes (DM 2), obesity, arterial hypertension and lipid disorders in a well defined portion of the former Lubelskie Voivodship population amounting to 100–200 thousand people, with a random sample rate of 3–5% of the population aged over 35 years. 3 thousand people aged ≥ 35 years were selected from among the inhabitants of the Lublin Region villages and from the town of Lublin proportionally in age groups. The inhabitants of Lublin were examined in Primary Health Care Department of Lublin Medical University and in local outpatients clinics, the handicapped were examined in their households. Villagers were examined in local health centres by a doctor and nurse team from Primary Health Care Department of Lublin Medical University. Medical history of patients was taken also with reference to the history of metabolic diseases in the family, triple measurement of resting arterial blood pressure was performed within 10 minutes, weight (on medical scales) and height were measured. Fasting blood samples were taken from the basilic vein to determine the levels of whole blood glucose and total cholesterol as well as HDL cholesterol and triglycerides in blood serum. Breakdown into weight categories was performed on the basis of the BMI index according to the WHO classification, assuming the values of < 18.5 for underweight, 18.5 – 24.9 for normal weight, 25.0 – 29.9 for overweight, 30.0 – 39.9 for obesity and ≥ 40.0 for “monstrous” obesity. Blood pressure values $\geq 140/90$ mmHg during at least two measurements were classified as arterial hypertension. Patients with no earlier diabetes diagnosis and whose fasting glycaemia did not exceed 8 mmol/l were submitted to oral glucose load test of 75 g of glucose and their blood glucose level was taken 2 hours after the test. Blood glucose level was determined by means of the Glucotrend glucometer produced by Roche. Consistency of the results obtained with the glucometer with the results obtained by means of laboratory tests was proved in comparative checks. Glycaemia was evaluated according to the WHO criteria from 1985 (15). DM 2 was diagnosed when the full blood fasting glycaemia value was ≥ 6.7 mmol/l (120 mg/dl) and/or in the 120th minute after the glucose load ≥ 10 mmol/l (180 mg/dl). Impaired glucose tolerance (IGT) was diagnosed when the fasting glycaemia value was < 6.7 mmol/l (120 mg/dl) and was between ≥ 6.7 mmol/l (120 mg/dl) and < 10 mmol/l (180 mg/dl) in the 120th minute after the glucose load. Total cholesterol, HDL-cholesterol and TG were determined by means of the enzymatic method with Cormay tests. LDL-cholesterol (low density lipoprotein cholesterol) (LDL-chol.) was calculated with the Friedewald formula. The following values were assumed as pathological: total cholesterol ≥ 5.2 mmol/l (200 mg/dl), LDL-cholesterol ≥ 3.5 mmol/l (135 mg/dl), HDL-cholesterol < 1 mmol/l (39 mg/dl) for women and < 0.9 mmol/l (35 mg/dl) for men, TG ≥ 2.3 (200 mg/dl) – according to the American Heart Association’s recommendation (1), TG ≥ 1.7 mmol/l – according to the guidelines of Zimmet and Alberti. 3 782 persons were examined (63% randomly chosen), out of which 1 809 in the countryside (60.3% of the randomly chosen) and 1 973 in the town (65.8% of

the randomly chosen). DM 2 was found in 17.6% of the examined from villages and 14.1% from the town (newly diagnosed diabetes amounted to 75% in the countryside and 56% in the town). Obesity (BMI ≥ 30 kg/m²) was found in 30.8% of subjects from villages and in 30.1% of town dwellers. Arterial hypertension (RR $\geq 140/90$ mmHg) was diagnosed in 69.4% villagers and in 68.6% people from the town. The total cholesterol in serum value of ≥ 5.2 mmol/l (200mg/dl) was found in 66.4% of the examined from the countryside and 60% from the town, LDL cholesterol levels ≥ 3.5 mmol/l (135mg/dl) were found in 57.3% and 52.6% respectively, and triglycerides levels ≥ 2.3 mmol/l (200mg/dl) in 15.1% villagers and in 22% of town dwellers. In accordance with Zimmet's recommendation TG > 1.7 mmol/l (150mg/dl) was found in 33.3% of the examined from the countryside and in 44.8% from the town. In the countryside hypo-HDL-cholesterolemia was found in 21.7% of subjects and in 31.4% of the examined in the town (7).

DISCUSSION

It has been known from ancient times that excessive eating and drinking is associated with obesity, gout, and cerebral stroke. Studying history, we can find a number of famous persons (Henry VIII – king of England, Bismarck – Prussian Chancellor, John III Sobieski – King of Poland, and many others) who, according to contemporary diagnosis, developed metabolic syndrome. A significant change in the way of life of many ethnic groups of nations, or at least parts of societies in particular countries, has taken place since the beginning of the 20th century. Generally speaking, these changes consist mostly in the transition from low-caloric diet that was mostly formed by food rich in starch and dietary fibre and small amounts of fat and protein and requiring significant physical amount, to the diet with an excess of calories, mostly from animal fat and beet sugar and the 'sitting' way of life.

Similar changes take place in Poland also including the examined inhabitants of towns and villages of the Lublin Region. A couple of decades ago, the inhabitants of this region situated in the east part of Poland were mostly farmers. In recent decades these proportions have changed to the benefit of town dwellers. The elderly people die in the countryside, the young ones move to towns. At the same time the character of work in this region also changes. Hard physical human labour is replaced by machine work, inhabitants of the region more and more frequently leading a 'sitting' life. But they still have not managed to fall into a habit of purposeful physical activity outside their workplaces. As a rule they nourish in a way that is traditional for this area: meat (mostly pork) and fat - rich diet containing large amounts of beet sugar.

In the situation where the number of subjects with metabolic syndrome grows, it is surprising that the data on prevalence of type 2 diabetes, which is a basic element of this syndrome, refer mostly to developing countries and among the developed countries only the USA has credible data on the diabetes prevalence (6). The results of our study as well as the research of the Krakow Group lead by Prof. Zbigniew Szybiński (14) and the Lodz Group led by Prof. Józef Drzewoski (3), stress unexpectedly large prevalence of diabetes and impaired glucose tolerance in the populations of particular towns (Krakow, Lublin, Lodz) and villages (Lublin Region) in Poland. Apart from diabetes, also very significant prevalence of obesity, arterial hypertension, and lipidaemic disorders were found in these three examined groups of people (3,7,14). From the recently quoted Australian data, it results that the prevalence of DM2 and other categories of impaired glucose tolerance is growing there very rapidly (4).

While starting to write this publication, its authors planned to present in a single article their theoretical knowledge as well as the research and experience from their daily practice in the field of metabolic syndrome. Based on our experience, we want to present to family doctors a plan of action – the most rational in our opinion – in the Polish circumstances: a plan of active prevention, diagnosis, and best possible treatment of various components of the syndrome, especially obesity, arterial hypertension, lipidaemic disorders, DM 2 and, as a result, occurrence

of clinically defined complications of arteriosclerosis, ischaemic heart disease, central nervous system ischaemia, ischaemic limbs, and other less frequent complications. Puttering so much information in just one article seemed too dangerous to us; there was a danger of simplifying the presented considerations. An idea occurred to us to present our considerations in two parts: a/ historical and theoretical, b/ purely practical one. This was the first article. The other one entitled *Metabolic Syndrome in doctor's daily practice* was sent to the editors of "Polish Family Medicine" Journal and it was accepted.

REFERENCES

1. Aktualne stanowisko American Heart Association. Ogólne zalecenia American Heart Association dotyczące prewencji pierwotnej chorób sercowo-naczyniowych. Med. Prakt., wyd. spec., 3, 87, 1998.
2. Cambell I.W., Purcell H.: The silent sextet. Br. J. Diabetes Vasc. Dis., 1, 3, 2001.
3. Drzewoski J. et al.: Występowanie cukrzycy typu 2 i wybranych zaburzeń metabolicznych w populacji miejskiej osób dorosłych powyżej 35 roku życia. Pol. Arch. Med. Wew., CVI, 3, 9, 787, 2001.
4. Dunstan D. W. et al.: The rising prevalence of diabetes and impaired glucose tolerance. Diabetes Care, vol. 25, 829, 2002.
5. Hanefeld M., Leonhardt W.: The Metabolic Syndrome. Gustav Fischer Verl., Jena 1997.
6. Harris M.I. et al.: Prevalence of impaired fasting glucose, and impaired glucose tolerance in U.S. adults: the Third National Health and Nutrition Examination 1988-1994. Diabetes Care, 21, 518, 1998.
7. Łopatyński J. et al.: Badania nad występowaniem cukrzycy typu 2 w populacji powyżej 35 roku życia na wsi i w mieście w regionie lubelskim. Pol. Arch. Med. Wew., CVI, 3, 37, 2001.
8. Łopatyński J. et al.: Morbidity in adult rural population in Lublin region. Results from own health examination survey. Annales UMCS, sectio D, vol. 53, suppl. 5, 156, 1999.
9. Łopatyński J.: Badania nad wskaźnikami przemiany lipidowej, tolerancja glukozy oraz sekrecją insuliny i glukagonu w przebiegu zachowawczego leczenia tyreotoksykozy. Endokryol. Pol., 32, 287, 1981.
10. Mardarowicz G., Łopatyński J.: The thyrotoxic patients as weight cyders. The 15 yr long follow-up study of metabolic outcomes Int.J. Obes., vol 22, suppl. 3, 251, 1998.
11. Mardarowicz G.: Leczenie tyreostatyczne a zagrożenie powikłaniami miażdżycy tętnic. Pr. dokt., 1982.
12. Reaven G.M.: Banting Lecture 1988. Role of insulin resistance in human disease. Diabetes, 37, 1595, 1988.
13. Rywik S. et al.: Założenia metaboliczne „Eksperymentu Polskiego” Pierwotnej Prewencji Choroby Wieńcowej. Przegl. Lek., 32, 510, 1975.
14. Szurkowska M. et al.: Chorobowość z powodu cukrzycy typu 2 w populacji Krakowa, Pol. Arch. Med. Wew., CVI, 3, 9, 771, 2001.
15. World Health Organisation: Diabetes Mellitus: Report of WHO Study Group. WHO Geneva, Technical Report Series, 727, 1985.
16. World Health Organisation: Part 1. Definition, Diagnosis and Classification of Diabetes Mellitus and its complications. Tech. Rep. WHO Geneva, 1999.

SUMMARY

The authors present the history of selecting and understanding the essence of the metabolic syndrome (X syndrome, Reaven's syndrome) related to insulin resistance as well as

its contemporary working definition allowing diagnosing affected individuals. They describe the cycle of their own study investigating the prevalence of metabolic syndrome elements in patients treated because of their thyreotoxicosis. It has been observed that 4 weeks after thyreostatic treatment is started, many of these patients are affected by the growth of their body mass and total cholesterol level (mostly at the cost of LDL-cholesterol). After 2 years the growth of body mass is significant, many patients develop arterial hypertension. After 15 years of obesity, diabetes type 2 (DM2), arterial hypertension, dyslipidaemia, hyperinsulinaemia and full metabolic syndrome are found much more frequently than in the control group. In the research carried in the 1987–1989 period, we found the following in 11 546 subjects from the Lublin region (villagers aged over 18): overweight in 36% women and 34% of men, and obesity in 30% of women and 10% of men, and arterial hypertension in 24.2% and DM 2 in 2.7% of the whole examined group. Within the research carried out between 1998 and 2000 we examined 3 782 persons (63%) out of 6 000 persons aged over 35 carefully selected from the Lublin town and the Lublin region villages. DM 2 was found in 17.6% of the examined in the countryside and in 14.1% from the town (newly diagnosed diabetes – 75% and 56% respectively). Obesity (BMI ≥ 30 kg/m²) was found in 30.8% of the examined from villages and 30.1% town dwellers, arterial hypertension (RR $\geq 140/90$ mmHg) was found in 69.4% villagers and 68.6% subjects from the town. Total serum cholesterol ≥ 5.2 mmol/l (200mg/dl) was found in 66.4% of the examined from the countryside and in 60% from the town, LDL-cholesterol ≥ 3.5 mmol/l (135mg/dl) was found in 57.3% and 52.6% respectively, and triglycerides ≥ 1.7 mmol/l (150mg/dl) in 33.3% and 44.8% respectively. Hipo-HDL-cholesterolaemia was found in 21.7% of the examined from villages and in 31.4% of the examined from Lublin. 76.5% of the examined from the countryside and 72.7% from the town had a raised WHR index.

Nasze badania nad zespołem metabolicznym

Autorzy przedstawiają historię wyodrębnienia i rozumienia istoty zespołu metabolicznego (zespołu X. zespołu Reavena) związanego z insulinopornością i jego współczesną roboczą definicję, pozwalającą na postawienie rozpoznania u dotkniętych nim osobników. Opisują cykl własnych prac, badających występowanie elementów zespołu metabolicznego u chorych leczonych z powodu tyreotoksykozy. Zaobserwowano, że po 4 tygodniach leczenia tyreostatycznego u wielu z nich dochodzi do wzrostu masy ciała i stężeń cholesterolu całkowitego (głównie kosztem wzrostu LDL-cholesterolu). Po 2 latach wzrost masy ciała jest znaczny, u wielu pojawia się nadciśnienie tętnicze. Po 15 latach znacznie częściej niż w grupie kontrolnej pojawiają się otyłość, cukrzyca typu 2 (DM 2), nadciśnienie tętnicze, dyslipidemia, hyperinsulinemia i pełnoobjawowy zespół metaboliczny. W badaniach przeprowadzonych w latach 1987–1989 u 11546 kolejno zgłaszających się mieszkańców wsi lubelskiej (powyżej 18 roku życia) stwierdziliśmy: nadwagę u 36% kobiet i 34% mężczyzn, otyłość u 30% kobiet i 10% mężczyzn, a w całej grupie badanych nadciśnienie tętnicze u 24,2%, DM 2 u 2,7%. W badaniach przeprowadzonych w latach 1998–2000 oceniono 3782 osoby (63%) z 6000 wylosowanych mieszkańców Lublina i wsi lubelskiej powyżej 35 roku życia. Stwierdzono DM 2 u 17,6% badanych na wsi i u 14,1% w mieście (cukrzyca nowo wykryta stanowiła odpowiednio 75% na wsi i 56% w mieście). Otyłość (BMI ≥ 30 kg/m²) stwierdzono u 30,8% mieszkańców wsi i u 30,1% mieszkańców miasta. Nadciśnienie tętnicze (RR $\geq 140/90$ mmHg) stwierdzono u 69,4% badanych na wsi i u 68,6% badanych w mieście. Stężenie cholesterolu całkowitego w osoczu $\geq 5,2$ mmol/l (200mg/dl) stwierdzono u 66,4% badanych ze wsi i 60% z miasta, cholesterol LDL $\geq 3,5$ mmol/l (135md/dl) odpowiednio u 57,3% i 52,6%, a trójglicerydów $\geq 1,7$ mmol/l (150md/dl) odpowiednio u 33,3% mieszkańców wsi i 44,8% mieszkańców miasta. Hipo-HDL-cholesterolemię stwierdzono na wsi u 21,7%, a w mieście u 31,4% badanych. 76,5% badanych na wsi i 72,7% w mieście miało zawyżony wskaźnik WHR.