Influence of obesity on biological age in patients with arterial hypertension

Olena Kolesnikova, Olga Zaprovalna, Tetiana Bondar, Anna Potapenko

L.T. Mala Therapy National Institute of the National Academy of Medical Sciences of Ukraine, Kharkiv, Ukraine

Abstract

Background: The aim of this study was to establish the relationship between metabolic disorders, overweight and obesity with markers of accelerated ageing in patients with hypertension.

Materials and methods: One hundred sixteen patients (the age 35–65 years, women 62.3%) with stage 1–2 grade 1–2 hypertension and low/moderate cardiovascular risk (CVR) were included in the study. 34 patients (27.59%) were obese, 50 patients (43.1%) were overweight, 32 patients (29.31%) had normal weight. Anthropometric, clinical, biochemical and molecular genetic methods (relative telomere length (RTL-b), telomerase activity (TA) and 5-methylcytosine global methyl level (GML) in DNA of blood mononuclear cells) were used. Epigenetic age was calculated using the DNAm PhenoAge epigenetic clock.

Results: The increase markers of carbohydrate metabolism [glycated haemoglobin (HbA_{1c}), fasting plasma glucose (FPG), insulin, homeostasis model assessment of insulin resistance (HOMA-IR)], changes of lipid metabolism indicators [an increase in triglycerides (TG) and a decrease in high-density lipoprotein cholesterol (HDL)] were revealed in the obese group, compared with the normal weight group ($p < 0.05$). We didn't find differences in RTL-b in any groups ($p > 0.05$). But at the same time obese patients had higher GML and lower TA ($p < 0.05$). The accelerated ageing (by DNAm PhenoAge epigenetic clock) was association with higher visceral fat%, higher levels, TG, very low-density lipoprotein cholesterol, all parameters of carbohydrate metabolism (HbA_{1c}, FPG, Insulin, HOMA-IR) and lower HDL-C ($p < 0.05$).

Conclusions: Pathological weight gain associated with the progression of metabolic disorders and accelerated ageing in patients with hypertension and low/moderate cardiovascular risk.

Key words: overweight; obesity; arterial hypertension; epigenetic age; accelerated ageing

Arterial Hypertens. 2023, vol. 27, no. 2, pages: 88–98
DOI: 10.5603/AH.a2023.0001

Introduction

Obesity is one of the largest public health challenges of this century worldwide [1, 2]. According to report of World Health Organization in 2016, the number of adults living with overweight reached 1.9 billion, which corresponds to 39% of the global adult population, of whom 650 million exhibited obesities [1]. Another important health problem is an increase in the number of older people in the world [3, 4]. There is evidence that ageing, and obesity are interrelated and may influence each other [5, 6]. An increase in body weight can trigger the processes of accelerated ageing and thus contribute to the progression of metabolic and age-associated diseases [7].

Address for correspondence: Olena Kolesnikova, L.T. Mala Therapy National Institute of the National Academy of Medical Sciences of Ukraine, 2 a, Lyubovi Maloy ave., Kharkiv, 61039, Ukraine, tel: + 380 50 169 9696; e-mail: kolesnikova1973@gmail.com

Despite the large number of new developments in both dietary therapy and drug treatment, the number of obese patients, according to the National Task Force on Treatment of Obesity, is increasing in all age groups [8]. It's mainly related to lifestyle, which is characterized by an extremely high-calorie diet and a lack of motor activity. Today it is especially important, so that obesity is a significant risk factor for cardiovascular disease and type 2 diabetes [9, 10]. According to WHO data, overweight and obesity contribute to the development of up to 44–57% of cases of type 2 diabetes, 17–23% of cases of coronary heart disease, 17% of hypertension, 30% of gallstone disease, 14% of osteoarthritis, and 11% of malignant tumours [1]. These diseases have a clear association with age. With accelerated ageing, there is an early decline in adaptive mechanisms of all physiological systems of the body, there is a significant decrease in physical and mental activity, which contributes to the early development of age-related pathology.

Accelerated ageing is determined by biological age (BA) [11, 12]. One may discuss accelerated ageing if the biological age is ahead of the chronological age (ChA). BA is the correspondence of an individual morphofunctional level to some average statistical norm of a given population, which reflects the unevenness of development, maturity and ageing of various physiological systems and the rate of age-related changes in the adaptation of the body's capabilities. The reasons for different rates of ageing can be genetic and epigenetic factors, as well as environmental factors. It is not possible to accurately determine the beginning of old age based on biological characteristics, since individuals with the same calendar age are not always the same age biologically [13, 14]. Thus, BA serves as an assessment of the individual age status of the organism.

Telomere length is considered one of the markers of biological ageing [15-17]. Telomeres are structures located at the ends of chromosomes and progressively decrease with each cell division. Telomere length plays a key role in preserving genomic stability. Telomere length is a balance between processes that shorten telomeres during cell division with incomplete DNA replication, and processes that lengthen telomeres under the action of telomerase, an RNA-protein complex that adds telomeric repeats to the ends of DNA molecules. Ageing, inflammation, and oxidative stress accelerate the process of telomere shortening [18, 19]. Telomerase counteracts this process, maintaining and lengthening the length of telomeres. Telomerase activity and telomere length play a decisive role in cellular aging and in the pathobiology of several human diseases. Recent studies have shown that the telomere length can be changed under the influence of genetic and epigenetic factors, sex hormones, active forms of oxygen, and inflammatory reactions. Telomere length is often shorter in obese patients. In people with obesity, excess adipose tissue plays a key role in the development of a chronic and systemic inflammatory condition, which can cause a shortening of telomere length. There are emerging data indicating a bidirectional relationship between telomere length and obesity. Obese patients show signs of increased inflammation, oxidative stress, and premature ageing [20–22].

Since multiple attempts to develop generally accepted standards for measuring BA have not been successful, recently epigenetic age has attracted the most attention as the one that most accurately reflects the ageing process [23]. Its measurement is based on changes in the DNA methylation profile that occur throughout life at specific locations along the genome. Although a person's epigenetic age correlates with their ChA, there are some exceptions. For example, the epigenetic age of long-lived people is significantly younger than their life expectancy [24]. Diet, lifestyle, and environmental exposures can induce epigenetic changes throughout a person's lifetime, influencing health and disease occurrence. For example, epigenetic processes are disrupted in such diseases as cancer and Alzheimer's disease [23]. This is extremely important, since scientific evidence indicates that epigenetic changes can affect not only the life of a given person, but also be transmitted from generation to generation [25].

DNA methylation creates a biological record of various molecular processes involved in the development, maintenance and decline of an individual, contributing to age-related diseases [23]. S. Horvath, analysing the data of 13 long-term studies on the study of the DNA methylation profile, found that an increase in epigenetic age relative to ChA increases the risk of mortality, regardless of other known risk factors. It was shown that the ≈5% of people who aged significantly faster than others (the epigenetic age was more than 10 years higher than the ChA) had an almost 50% increase in the risk of death. Such informational value of epigenetic age in predicting life span has raised the question of establishing biomarkers that can help to establish accelerated ageing in time without the use of complex molecular genetic methods. Further research in this direction led to the establishment of a lot of markers that are likely to be correlated with DNA methylation. Thus, several ageing-related epi-

genetic clocks have recently been proposed to predict BA [25]. Epigenetic clocks may provide a means to establish differential rates of ageing [25–27].

The aim of this study was to establish the relationship between metabolic disorders, overweight and obesity with markers of accelerated ageing BA age in patients with hypertension.

Material and methods

Characteristics of study participants

The study population consisted of 116 patients (the age 35–65 years, women 62.3%) with stage 1–2 grade 1–2 hypertension and low/moderate cardiovascular risk (CVR). The diagnosis and treatment of hypertension was made on the basis of 2020 International Society of Hypertension Global Hypertension Practice Guidelines. All patients received standard antihypertensive therapy [angiotensin-convertase enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB), dihydropyridine-calcium channel blocker, thiazide-like diuretic). Twenty healthy volunteers (hereinafter — controls) aged 35–65 years, were also included in the study. All patients and volunteers signed the informed consent to participate in the study. The research protocol was approved at a meeting of the Ethics Commission of the L.T. Mala NIT NAMSU. Physical examination of patients included measurements of height, body weight, waist circumference (WC) and hip circumference (HC), body mass index (BMI) calculation and waist-to-hip ratio (WC/HC) calculation. Body composition was determined by the bioelectrical impedance method using Composition Monitor BF511, Omron; body fat percentage (FAT, %), skeletal muscle percentage (MUS, %), visceral fat level (VIS, %). Office BP was measured in accordance with 2020 International Society of Hypertension Global Hypertension Practice Guidelines. Complete blood test was done in all patients. Lipid metabolism was assessed by total cholesterol (TC), triglycerides, low density lipoprotein cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C) and high density lipoprotein cholesterol (HDL-C). Carbohydrate metabolism was assessed by measuring fasting blood glucose (FPG), glycated haemoglobin (HbA_{1c}) and insulin levels. Insulin resistance (IR) was determined by the homeostasis model assessment of insulin resistance (HOMA-IR) calculation. The state of the prooxidant system was evaluated by the levels of total hydroperoxide (THP) content, and the state of antioxidant protection system — by total antioxidant activity (TAA), THP to TAA ratio (THP/TAA) calculation. Determination of global DNA methylation (GML) by the percentage content of 5-methylcytosine (5-mc) in the DNA of blood mononuclear cells was carried out by the immunoenzymatic method using the set of reagents "5-mc DNA ELISA Kit" (Zymo Research Corp., United States). The sensitivity of the method is 0.5% 5 mC/100 ng of DNA.

Telomere length was determined by real-time PCR. Amplification was performed using SsoAdvanced Universal SYRB Green Supermix (BioRad Laboratories, USA) and primer system (Thermo Fisher Scientific). The relative length of telomeres (RTL-b) was determined by the T/S ratio (T — the number of copies of telomeric repeats, S — the number of copies of the 36B4 gene), followed by normalization of the obtained data to the reference sample, which was included in each experiment. Telomerase activity was determined by real-time PCR using the TRAPeze Kit RT Telomerase Detection Kit (Millipore, United States).

Epigenetic age was calculated using the DNAm PhenoAge epigenetic clock based on nine biological markers (albumin, g/L; creatinine, mg/dL; glucose mg/dL; C-reactive protein (CRP) mg/L, lymphocytes, %; red cell dist width (RCDW), %; mean cell volume (MCV); alkaline phosphatase U/L; leukocytes, $x10^9$; age, years).

Continuous variables obtained from the participants in this study were expressed as means ± standard deviations (SDs). Categoric variables were expressed as percentages. Data were compared using Student's t-test (for parametric continuous variables) and the Mann-Whitney U test (for non-parametric continuous variables) and chi-square test with Yates's correction (for categoric variables). To assess the interrelationship of indicators, a correlation analysis was performed with the calculation of pairwise correlation coefficients. Also, the associations between variables were assessed using linear multiple regression models. When estimating regression equations, the method of stepwise inclusion of predictors was used, which ranks features in accordance with their contribution to the model. P values < 0.05 were considered statistically significant. All analyses were conducted via the statistical package Statistica V10.0.

Results

A comparative analysis showed that our patients with hypertension are accompanied by significant changes in the main metabolic parameters compared with the control group (Tab. 1). This fact confirmed

Table 1. Comparative assessment of indicators of the main and control groups

Indicators	Main group (n = 116)	Control group (n = 20)	M-W p-level
	M ± σ	M ± σ	
Age [years]	47.96 ± 11.86	48.61 ± 6.08	0.840
Weight [kg]	79.96 ± 14.86	67.11 ± 5.00	0.002
BMI [kg/m^2]	27.71 ± 4.54	22.71 ± 1.23	0.0001
WC [sm]	90.67 ± 12.72	84.64 ± 5.49	0.083
HC [sm]	103.02 ± 9.86	96.54 ± 3.70	0.016
WC/HC	0.88 ± 0.13	0.88 ± 0.07	0.903
HR [b.p.m.]	69.78 ± 9.05	65.45 ± 4.82	0.0387
SBP [mm Hg]	125.71 ± 17.46	116.52 ± 9.87	0.0235
DBP [mm Hg]	79.26 ± 10.85	72.18 ± 6.47	0.0053
HbA_{1c} (%)	5.67 ± 0.55	5.08 ± 0.25	0.0002
FPG [mmol/L]	5.57 ± 1.28	5.05 ± 0.31	0.1284
Insulin [mMU/L]	21.57 ± 13.90	9.69 ± 1.19	0.0018
HOMA-IR	5.39 ± 4.04	2.18 ± 0.30	0.0036
TC [mmol/L]	5.61 ± 1.15	4.54 ± 0.35	0.0007
TG [mmol/L]	1.48 ± 0.79	0.84 ± 0.15	0.0033
VLDL-C [mmol/L]	0.68 ± 0.39	0.42 ± 0.11	0.0130
HDL-C [mmol/L]	1.36 ± 0.32	1.37 ± 0.17	0.9621
LDL-C [mmol/L]	3.7 ± 1.03	2.79 ± 0.45	0.0054
Uric acid [μmol/L]	271.52 ± 78.34	247.36 ± 45.78	0.2605
TAA [μmol trolox equivalent]	603.69 ± 25.58	538.09 ± 156.75	0.1234
THP [μmol/L]	80.14 ± 11.39	131.37 ± 51.96	0.0004
THP/TAA [un]	0.13 ± 0.02	0.29 ± 0.23	0.0112

BMI — index body mass; WC — waist circumference; WC/HC — waist-to-hip ratio; HR — heart rate; SDP – systolic blood pressure; DBP – diastolic blood pressure; HbA_{1c} — glycated haemoglobin; FPG — fasting plasma glucose; HOMA-IR — homeostasis model assessment of insulin resistance; TC — total cholesterol; TG — triglycerides; VLDL-C — very low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TAA — total antioxidant activity; THP — total hydroperoxides

that even the initial stages of hypertension and low CVR are accompanied by metabolic disorders.

To clarify the influence of age characteristics, a separate analysis of indicators was carried out between the main and control groups in the age ranges up to 45 years and 45–65 years. Differences between the hypertensive and the control group in each age range were the same as for the group as a whole. We had only one exception: fasting glucose level (FPG) in the younger group (up to 45 years), in contrast to older patients, were the same in patients of both control and hypertensive groups, which may indicate an age-dependent progression of carbohydrate disorders.

Deviation of anthropometric characteristics from control values, and signs of impaired carbohydrate and lipid metabolism were observed in patients with hypertension in both age groups and their degree increased with age.

Analysis of weight characteristics by BMI revealed that among patients with hypertension (n = 116), 34 patients (27.59%) were obese, 50 patients (43.1%) were overweight, and only 32 patients (29.31 %) had normal weight. All patients in the control group were of normal weight (BMI less than 25).

The analysis of weight characteristics was carried out in patients of younger and older age groups separately (Fig. 1, Tab. 2,).

Comparison of age groups revealed that with increasing age, there is a decrease in the number of patients with normal weight and an increase in the number of overweight and obese patients.

There were no significant age differences of BMI in patients with overweight and obesity. At the same time, the BMI of patients with normal weight in the younger group was significantly lower compared to the older group.

To assess the impact of obesity, we conducted a comparative analysis of metabolic parameters depending on weight status (Tab. 3).

The measurement of anthropometric parameters revealed the expected increase in WC, HC,

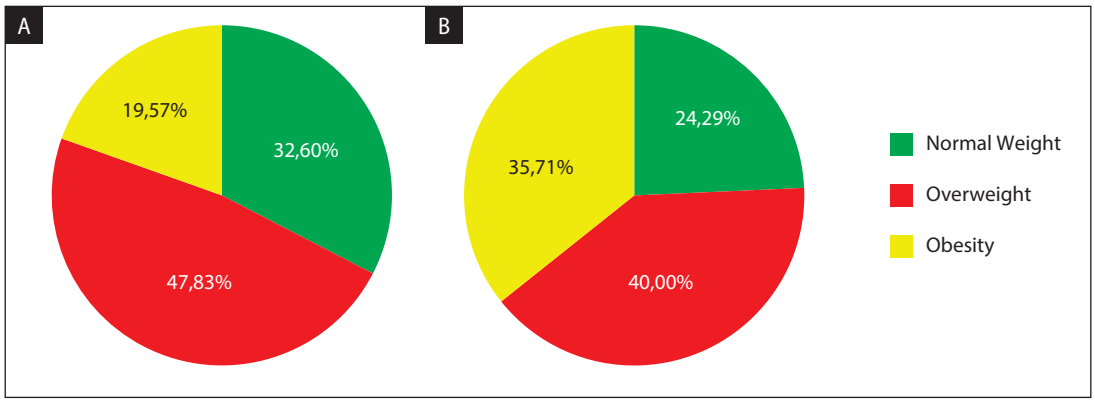

Figure 1. Obesity by body mass index (BMI) in patients with hypertension in the different age group. **A**. In the younger group (up to 45 years); **B**. In the older group (45–65 years)

Table 2. Body mass index (BMI) in patients with hypertension in the different age group

Indicators	Up to 45 year (n = 46)	45–65 year (n = 70)	p-value
Normal weight [kg]	21.39 ± 1.32	22.83 ± 1.69	0.012
Overweight [kg]	27.52 ± 1.44	27.70 ± 1.40	0.674
Obesity [kg]	32.75 ± 2.48	32.87 ± 3.77	0.845

Table 3. Indicators in patients depending on weight status by body mass index (BMI)

Indicators	Normal weight (n = 32)	Overweight (n = 50)	Obesity (n = 34)	P1–2	P1–3	P2–3
	1	2	3			
BMI [kg/m^2]	22.15 ± 1.68	27.56 ± 1.41	32.84 ± 3.44	0.1802	0.0000	0.0000
FAT (%)	26.76 ± 6.58	29.92 ± 7.92	37.24 ± 8.58	0.0843	0.0000	0.0002
MUS (%)	30.84 ± 4.48	30.37 ± 6.73	27.16 ± 5.17	0.3546	0.0045	0.0289
VIS (%)	6.41 ± 1.76	8.47 ± 2.61	12.13 ± 11.16	0.0000	0.0085	0.0330
WC [sm]	77.33 ± 7.00	90.26 ± 8.52	104.09 ± 8.12	0.0000	0.0000	0.0000
HC [sm]	94.47 ± 5.77	103.18 ± 5.89	110.79 ± 11.69	0.0000	0.0000	0.0002
WC/HC	0.82 ± 0.07	0.87 ± 0.07	0.96 ± 0.20	0.0012	0.0004	0.0097
HR [b.p.m.]	72.36 ± 10.65	67.80 ± 6.96	71.24 ± 10.25	0.0442	0.6835	0.0859
SBP [mm Hg]	119.56 ± 16.18	125.92 ± 13.01	132.62 ± 16.78	0.0206	0.0040	0.0411
DBP [mm Hg]	74.36 ± 9.51	80.76 ± 11.46	84.38 ± 11.91	0.0147	0.0010	0.1619
HbA_{1c} (%)	)5.44 ± 0.60	5.71 ± 0.60	5.80 ± 0.40	0.1199	0.0233	0.5518
FPG [mmol/L]	5.31 ± 0.80	5.64 ± 1.73	5.72 ± 0.82	0.1601	0.0418	0.8032
Insulin [mMU/L]	16.37 ± 13.31	20.80 ± 12.01	27.63 ± 15.62	0.0284	0.0036	0.0306
HOMA-IR	3.93 ± 3.52	5.25 ± 3.98	7.08 ± 4.27	0.0123	0.0029	0.0594
TC [mmol/L]	5.41 ± 1.26	5.70 ± 1.08	5.69 ± 1.13	0.2154	0.3443	0.9087
TG [mmol/L]	1.08 ± 0.65	1.58 ± 0.77	1.69 ± 0.86	0.0010	0.0022	0.6506
VLDL-C [mmol/L]	0.49 ± 0.29	0.72 ± 0.34	0.82 ± 0.48	0.0011	0.0013	0.2775
HDL-C [mmol/L]	1.43 ± 0.35	1.35 ± 0.33	1.34 ± 0.28	0.2402	0.2547	0.9134
LDL-C [mmol/L]	3.49 ± 1.11	3.65 ± 1.02	3.54 ± 0.93	0.4310	0.8492	0.5777
Uric acid [μmol/L]	239.25 ± 85.28	278.73 ± 70.08	287.76 ± 75.45	0.0622	0.0170	0.6231
TAA [μmol trolox equivalent]	508.16 ± 187.11	571.05 ± 144.18	501.60 ± 136.50	0.2358	0.9025	0.1006

→

Table 3. Indicators in patients depending on weight status by body mass index (BMI)

Indicators	Normal weight (n = 32)	Overweight (n = 50)	Obesity (n = 34)	P1–2	P1–3	P2–3
	1	2	3			
THP [μmol/L]	108.00 ± 52.25	133.53 ± 41.78	153.94 ± 62.39	0.0032	0.0168	0.1661
THP/TAA [un]	0.31 ± 0.32	0.26 ± 0.12	0.37 ± 0.28	0.1453	0.5462	0.0501

BMI — index body mass; WC — waist circumference; WC/HC — waist-to-hip ratio; HR — heart rate; SDP – systolic blood pressure; DBP – diastolic blood pressure; HbA_{1c} — glycated haemoglobin; FPG — fasting plasma glucose; HOMA-IR — homeostasis model assessment of insulin resistance; TC — total cholesterol; TG — triglycerides; VLDL-C — very low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TAA — total antioxidant activity; THP — total hydroperoxides

Table 4. Ageing indicator in hypertensive patients depending on weight

Indicators	Normal weight (n = 32)	Overweight (n = 50)	Obesity (n = 34)	P1–2	P1–3	P2–3
	1	2	3			
Age, years	43.00 ± 11.55	46.67 ± 10.96	51.52 ± 8.30	0.0000	0.0010	0.0105
Phenoage, years	36.35 ± 13.25	42.59 ± 11.64	48.43 ± 9.62	0.0345	0.7827	0.0110
RTL-b, relative units	0.93 ± 0.33	0.93 ± 0.30	0.89 ± 0.19	0.8232	0.4217	0.7404
Telomerase activity	0.97 ± 0.55	0.88 ± 0.51	0.83 ± 0.47	0.5388	0.0001	0.6836
GML	2.77 ± 1.63	4.17 ± 1.93	4.74 ± 1.67	0.0401	0.0053	0.4250

RTL-b — relative telomere length of blood leukocytes; GML — 5-methylcytosine global methyl level

WC/HC, Vis% in patients with overweight and obesity, not only in comparison with a patient with normal weight but also among themselves ($p < 0.05$). BMI and FAT% in obese patients were significantly higher than in normal weight and overweight patients, while there was no difference between normal and overweight patients. Skeletal muscle percentage (MUS, %) was the same in normal weight and overweight groups but was decreased in obese patients compared to these groups.

The measurement of the office BP showed better control of SBP and DBP in normal weight patients ($p < 0.05$).

In the analysis of carbohydrate metabolism in the obese group, compared with the normal weight group, a significant increase in all indicators was found: HbA_{1c}, FPG, Insulin, HOMA-IR; in the overweight group, only Insulin and HOMA-IR differed significantly. Uric acid in patients of all groups was within the normal range, however, in patients with obesity, uric acid was significantly higher than in patients with normal weight. Patients with overweight and obesity also showed an increase in THP as an indicator of oxidative stress compared with patients of normal weight.

Evaluation of lipid metabolism indicators revealed an increase in triglycerides and a decrease in HDL in the overweight and obese groups compared with the normal weight group. It should be noted that these indicators were obtained in the absence of any lipid-lowering therapy at the initial examination at the moment of inclusion in the study. In the future, patients were prescribed lipid-lowering therapy in accordance with the 2019 European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the management of dyslipidaemias, and its results will be evaluated in further studies.

Thus, pathological weight gain associated to the progression of metabolic disorders. Patients with the same degree of hypertension and the same cardiovascular risk (CVR) had different degrees of metabolic disorders. Normal weight patients had minimal changes compared to obese patients.

To assess the rate of ageing measured by telomere length (RTL-b), telomerase activity (TA), global DNA methylation level (GML) and their association with weight status were analysed (Tab. 4). We didn't find differences in RTL-b in any groups. At the same time overweight and obese patients had higher GML and also TA was lower in obese patients ($p < 0.05$).

In order to determine association between ageing rates and weight, biological age was calculated using the DNAm PhenoAge epigenetic clock. After calculating the epigenetic age, the rates of ageing were determined for every object. If the patient's epigenetic age exceeded the chronological age by more than a year, the patient was classified as accelerated ageing, if less than or equal the patient was assigned to the group of healthy ageing. Analyse of associa-

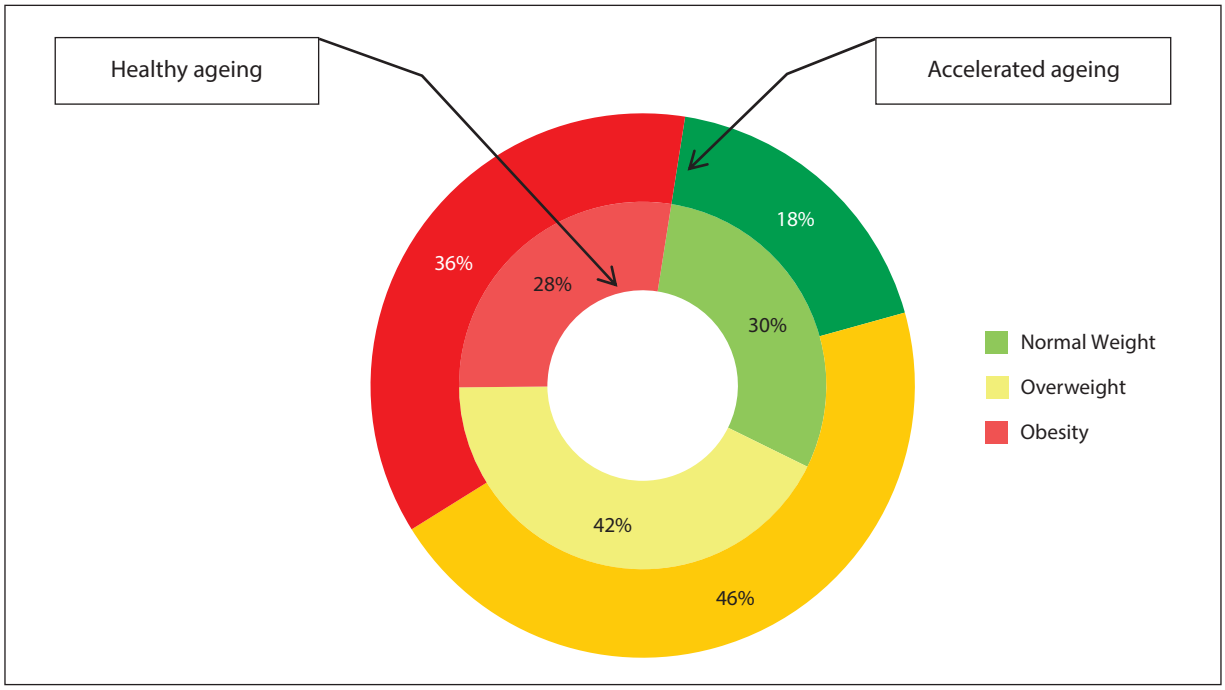

Figure 2. Weight status depending on the ageing rate

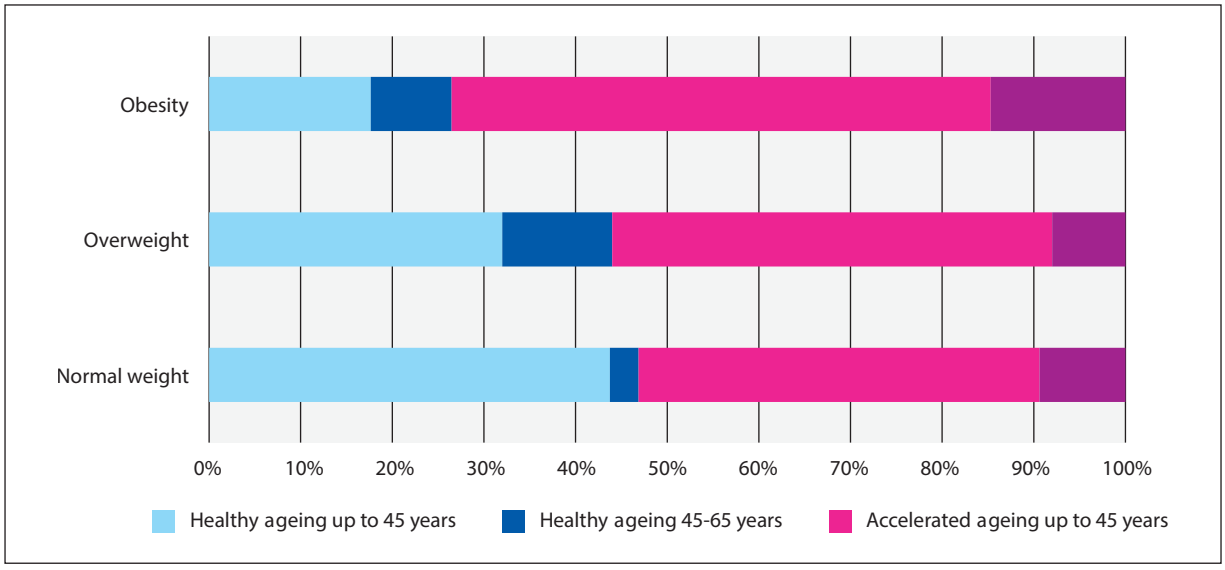

Figure 3. Ageing rate depending on weight in patients with hypertension

tion between ageing rate and weight is presented in the Figures 2, 3.

The comparative analysis to determine the factors influencing the rate of ageing was carried out between the accelerated and healthy ageing groups (Tab. 5). The accelerated ageing group had higher levels of Vis%, TG, VLDL-C, uric acid, and all parameters of carbohydrate metabolism (HbA_{1c}, FPG, Insulin, HOMA IR) and lower level of HDL-C.

Discussion

The relationship between obesity and ageing has attracted the attention of researchers for last decades. Metabolic dysregulation, oxidative stress, inflammation and immune dysfunction underlie not only obesity but also ageing and appear to be able to influence each other. It is known that metabolic disorders, including hyperglycaemia, insulin

Table 5. Characteristics of accelerated and healthy ageing groups

Indicators	Accelerated ageing	Healthy ageing	p-value
BMI [kg/m^2]	29.21 ± 5.01	27.38 ± 4.39	0.101
WC [sm]	96.43 ± 11.92	89.40 ± 12.59	0.428
HC [sm]	104.75 ± 10.38	102.65 ± 9.75	0.521
WC/H	0.92 ± 0.07	0.87 ± 0.14	0.260
Vis (%)	9.57 ± 3.99	8.94 ± 7.00	0.034
Fat (%)	30.25 ± 8.42	31.77 ± 8.81	0.432
Mus (%)	29.98 ± 5.93	29.15 ± 6.12	0.105
HbA_{1c} (%)	5.91 ± 0.51	5.62 ± 0.55	0.039
FPG [mmol/L]	6.58 ± 2.48	5.35 ± 0.65	0.000
Insulin [mMU/L]	27.38 ± 15.95	20.21 ± 13.11	0.037
HOMA-IR	7.66 ± 5.57	4.88 ± 3.45	0.004
TC [mmol/L]	5.51 ± 1.35	5.4 ± 1.10	0.560
TG [mmol/L]	1.77 ± 0.78	1.41 ± 0.78	0.020
VLDL-C [mmol/L]	0.86 ± 0.49	0.65 ± 0.36	0.023
HDL-C [mmol/L]	1.19 ± 0.24	1.40 ± 0.33	0.002
LDL-C [mmol/L]	3.54 ± 1.21	3.58 ± 0.99	0.754
Uric acid [μmol/L]	328.82 ± 80.89	258.92 ± 72.27	0.001
TAA [μmol tr. equival.]	0.36 ± 0.26	0.28 ± 0.22	0.322
THP [μmol/L]	156.23 ± 68.28	124.44 ± 44.70	0.109
THP/TAA	496.55 ± 141.33	549.67 ± 159.95	0.206

BMI — index body mass; WC — waist circumference; WC/HC — waist-to-hip ratio; HR — heart rate; SDP – systolic blood pressure; DBP — diastolic blood pressure; HbA_{1c} — glycated haemoglobin; FPG — fasting plasma glucose; HOMA-IR — homeostasis model assessment of insulin resistance; TC — total cholesterol; TG — triglycerides; VLDL-C — very low-density lipoprotein cholesterol; HDL-C — high-density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; TAA — total antioxidant activity; THP — total hydroperoxides

resistance (IR) and hyperinsulinemia, dyslipidaemia, induce interconnected processes in the vessel wall and contribute to increased oxidative stress, apoptosis, and vascular permeability, contributing to cardiovascular ageing and increasing the risk of cardiovascular disease (CVD) and other age-related disease [28–31].

Importantly, advanced age is typically accompanied by increased fat deposition around the internal organs (visceral adipose tissue), in which adipocyte precursor cells (preadipocytes) tend to lose their specialized characteristics, undergo dedifferentiation, and acquire a senescent-like pro-inflammatory state; this results in increased production of proinflammatory cytokines and chemokines and induction of visceral adipose tissue inflammageing [32].

Given the etiological similarities between obesity and ageing, it is valid to speculate that obesity might accelerate the rate of ageing and the onset of age-related diseases [33]. Accordingly, obese mice have a shorter lifespan and increased levels of oxidative stress markers compared to their lean counterparts [34]. Likewise, extreme obesity is associated with substantially elevated rates of total mortality, with most of the excess deaths due to diseases typically associated with old age, including CVD [35]. Recently trial showed that obese individuals might lose up to 8 years of life compared to normal-weight individuals [36]. Remarkably, in rats, maternal obesity was found to accelerate the metabolic ageing of the offspring in a sex-dependent manner [37].

The similarities between obesity and age-related fat tissue dysfunction are also evidenced by the fact that multiple energy metabolism and energy-sensing pathways, as well as regulators of oxidative stress and inflammation, play similar roles in both obesity and ageing and their associated pathologies. These pathways represent potential druggable targets for both obesity and ageing [5].

It is known that the visceral type of obesity and the accumulation of senescent cells with an inflammatory phenotype lead to a high level of pro-inflammatory cytokines in the blood, which can interfere with the transmission of insulin signals. IR is often implicated as a cause of adverse ageing phenotypes and age-related conditions. It can even be assumed that counteracting IR can be an effective "anti-ageing" intervention.

In our study, differences in telomere length depending on the presence of excess weight and obe-

sity were not reliably confirmed. Perhaps this is due to the choice of the object of study (patients with low/moderate CVR). At the same time, an increase in telomerase activity in patients with obesity and a significant increase in GML in groups of overweight and obese patients may indicate an earlier start of ageing processes in these patients compared to patients with normal weight.

New therapeutic possibilities have emerged to influence the underlying pathological mechanisms of obesity. The similarity of the pathological processes between obesity and ageing: in cellularity, insulin sensitivity, secretory profiles, and the inflammatory state of adipose tissue [38, 39], allows us to hope for the success of similar interventions to eliminate dysfunctions associated with obesity and age-related pathology.

Conclusion

The results of our study showed that pathological weight gain associated to the progression of metabolic disorders and accelerated ageing. Patients with the same degree of hypertension and CVR had different degrees of metabolic disorders depending on body weight. The group of patients with normal weight not only had fewer metabolic changes compared to patients with obesity, but accelerated ageing was also less frequently observed among them.

Accelerated ageing can contribute to the rapid progression of obesity and other age-related pathologies. Assessment of the relationship between accelerated ageing and obesity may be a determining tool for influencing health improvement and reducing morbidity and mortality rates of the population. Since many of the effects of ageing can be delayed or attenuated by lifestyle changes or currently available medications, research in this direction holds promise for improved risk prediction of various diseases associated with accelerated ageing of the population.

Acknowledgments

None.

Author's contributions

O.K.: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

O.Z.: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

T.B.: Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

A.P.: the acquisition of data for the work; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All authors read and approved the final manuscript.

Funding

None.

Availability of data and materials

Data and materials used and/or analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was conducted in accordance with the amended Declaration of Helsinki. The institutional review board approved the study, and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Obesity and overweight. https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight (Accessed 22/11 2019).
2. Bays HE, McCarthy W, Burridge K et al, Obesity Algorithm eBook, presented by the Obesity Medicine Association. www.obesityalgorithm.org. 2021. https://obesitymedicine.org/obesity-algorithm/.

3. Ageing and health. World Health Organization, 05 Feb 2018. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health..
4. Aging Well in the 21st Century: Strategic Directions for Research on Aging. NIA Strategic Directions, 2016, 35 pp. https://www.nia.nih.gov/sites/default/files/2017-07/nia-strategic-directions-2016.pdf..
5. Santos AL, Sinha S. Obesity and aging: Molecular mechanisms and therapeutic approaches. Ageing Res Rev. 2021; 67: 101268, doi: 10.1016/j.arr.2021.101268, indexed in Pubmed: 33556548.
6. Assmann KE, Ruhunuhewa I, Adjibade M, et al. The Mediating Role of Overweight and Obesity in the Prospective Association between Overall Dietary Quality and Healthy Aging. Nutrients. 2018; 10(4), doi: 10.3390/nu10040515, indexed in Pubmed: 29677164.
7. Lin YH, Chiou JM, Chen TF, et al. The association between metabolic syndrome and successful aging- using an extended definition of successful aging. PLoS One. 2021; 16(11): e0260550, doi: 10.1371/journal.pone.0260550, indexed in Pubmed: 34847175.
8. National Health and Nutrition Examination Survey 2017–March 2020 Prepandemic Data Files Development of Files and Prevalence Estimates for Selected Health Outcomes: National Center for Health Statistics (U.S.) NHSR National Health Statistics Reports URL No. 158. 2021 14 Jun. https://stacks.cdc.gov/view/cdc/106273.
9. Csige I, Ujvárosy D, Szabó Z, et al. The Impact of Obesity on the Cardiovascular System. J Diabetes Res. 2018; 2018: 3407306, doi: 10.1155/2018/3407306, indexed in Pubmed: 30525052.
10. Riaz H, Khan MS, Siddiqi TJ, et al. Association Between Obesity and Cardiovascular Outcomes: A Systematic Review and Meta-analysis of Mendelian Randomization Studies. JAMA Netw Open. 2018; 1(7): e183788, doi: 10.1001/jamanetworkopen.2018.3788, indexed in Pubmed: 30646365.
11. Diebel LWM, Rockwood K. Determination of Biological Age: Geriatric Assessment vs Biological Biomarkers. Curr Oncol Rep. 2021; 23(9): 104, doi: 10.1007/s11912-021-01097-9, indexed in Pubmed: 34269912.
12. Guerville F, De Souto Barreto P, Ader I, et al. Revisiting the Hallmarks of Aging to Identify Markers of Biological Age. J Prev Alzheimers Dis. 2020; 7(1): 56–64, doi: 10.14283/jpad.2019.50, indexed in Pubmed: 32010927.
13. Belsky DW, Moffitt TE, Cohen AA, et al. Eleven Telomere, Epigenetic Clock, and Biomarker-Composite Quantifications of Biological Aging: Do They Measure the Same Thing? Am J Epidemiol. 2018; 187(6): 1220–1230, doi: 10.1093/aje/kwx346, indexed in Pubmed: 29149257.
14. Jansen R, Han LKm, Verhoeven JE, et al. An integrative study of five biological clocks in somatic and mental health. Elife. 2021; 10, doi: 10.7554/eLife.59479, indexed in Pubmed: 33558008.
15. Yeh JK, Lin MH, Wang CY. Telomeres as Therapeutic Targets in Heart Disease. JACC Basic Transl Sci. 2019; 4(7): 855–865, doi: 10.1016/j.jacbts.2019.05.009, indexed in Pubmed: 31998853.
16. Schellnegger M, Lin AC, Hammer N, et al. Physical Activity on Telomere Length as a Biomarker for Aging: A Systematic Review. Sports Med Open. 2022; 8(1): 111, doi: 10.1186/s40798-022-00503-1, indexed in Pubmed: 36057868.
17. Amano H, Chaudhury A, Rodriguez-Aguayo C, et al. Telomere Dysfunction Induces Sirtuin Repression that Drives Telomere-Dependent Disease. Cell Metab. 2019; 29(6): 1274–1290.e9, doi: 10.1016/j.cmet.2019.03.001, indexed in Pubmed: 30930169.
18. Cheng F, Carroll L, Joglekar M, et al. Diabetes, metabolic disease, and telomere length. Lancet Diabetes Endocrinol. 2021; 9(2): 117–126, doi: 10.1016/s2213-8587(20)30365-x, indexed in Pubmed: 33248477.
19. Verma AK, Singh P, Al-Saeed FA, et al. Unravelling the role of telomere shortening with ageing and their potential association with diabetes, cancer, and related lifestyle factors. Tissue Cell. 2022; 79: 101925, doi: 10.1016/j.tice.2022.101925, indexed in Pubmed: 36137363.
20. Zhou Y, Hambly BD, McLachlan CS. FTO associations with obesity and telomere length. J Biomed Sci. 2017; 24(1): 65, doi: 10.1186/s12929-017-0372-6, indexed in Pubmed: 28859657.
21. Peña E, León-Mengíbar J, Powell TR, et al. Telomere length in patients with obesity submitted to bariatric surgery: A systematic review. Eur Eat Disord Rev. 2021; 29(6): 842–853, doi: 10.1002/erv.2865, indexed in Pubmed: 34545641.
22. Welendorf C, Nicoletti CF, Pinhel MA, et al. Obesity, weight loss, and influence on telomere length: New insights for personalized nutrition. Nutrition. 2019; 66: 115–121, doi: 10.1016/j.nut.2019.05.002, indexed in Pubmed: 31255876.
23. Field AE, Robertson NA, Wang T, et al. DNA Methylation Clocks in Aging: Categories, Causes, and Consequences. Mol Cell. 2018; 71(6): 882–895, doi: 10.1016/j.molcel.2018.08.008, indexed in Pubmed: 30241605.
24. Horvath S, Pirazzini C, Bacalini MG, et al. Decreased epigenetic age of PBMCs from Italian semi-supercentenarians and their offspring. Aging (Albany NY). 2015; 7(12): 1159–1170, doi: 10.18632/aging.100861, indexed in Pubmed: 26678252.
25. Horvath S. DNA methylation age of human tissues and cell types. Genome Biol. 2013; 14(10): R115, doi: 10.1186/gb-2013-14-10-r115, indexed in Pubmed: 24138928.
26. Quach A, Levine ME, Tanaka T, et al. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. Aging (Albany NY). 2017; 9(2): 419–446, doi: 10.18632/aging.101168, indexed in Pubmed: 28198702.
27. Salameh Y, Bejaoui Y, El Hajj N. DNA Methylation Biomarkers in Aging and Age-Related Diseases. Front Genet. 2020; 11: 171, doi: 10.3389/fgene.2020.00171, indexed in Pubmed: 32211026.
28. Salvestrini V, Sell C, Lorenzini A. Obesity May Accelerate the Aging Process. Front Endocrinol (Lausanne). 2019; 10: 266, doi: 10.3389/fendo.2019.00266, indexed in Pubmed: 31130916.
29. Zgheib NK, Sleiman F, Nasreddine L, et al. Short Telomere Length is Associated with Aging, Central Obesity, Poor Sleep and Hypertension in Lebanese Individuals. Aging Dis. 2018; 9(1): 77–89, doi: 10.14336/AD.2017.0310, indexed in Pubmed: 29392083.
30. Kolesnikova O, Potapenko A, Vysotska O, et al. Evaluation of hormonal and metabolic parameters, along with cardiovascular risk factors in women with non-alcoholic fatty liver disease combined with subclinical hypothyroidism depending on age. EUREKA: Health Sciences. 2021(1): 48–57, doi: 10.21303/2504-5679.2021.001618.
31. Shalimova A, Psarova V, Kochuieva M, et al. Features of hemodynamic and metabolic disorders in obese patients with resistant hypertension. Arterial Hypertens. 2020; 24(1): 22–29, doi: 10.5603/ah.a2020.0002.
32. Conte M, Martucci M, Sandri M, et al. The Dual Role of the Pervasive "Fattish" Tissue Remodeling With Age. Front Endocrinol (Lausanne). 2019; 10: 114, doi: 10.3389/fendo.2019.00114, indexed in Pubmed: 30863366.
33. Salmon AB. Beyond Diabetes: Does Obesity-Induced Oxidative Stress Drive the Aging Process? Antioxidants (Basel). 2016; 5(3), doi: 10.3390/antiox5030024, indexed in Pubmed: 27438860.
34. Zhang Y, Fischer KE, Soto V, et al. Obesity-induced oxidative stress, accelerated functional decline with age and increased mortality in mice. Arch Biochem Biophys. 2015; 576: 39–48, doi: 10.1016/j.abb.2014.12.018, indexed in Pubmed: 25558793.
35. Balayah Z, Alsheikh-Ali AA, Rashed W, et al. Association of obesity indices with in-hospital and 1-year mortality following acute coronary syndrome. Int J Obes (Lond). 2021; 45(2): 358–368, doi: 10.1038/s41366-020-00679-0, indexed in Pubmed: 32943761.
36. Grover SA, Kaouache M, Rempel P, et al. Years of life lost and healthy life-years lost from diabetes and cardiovascular dis-

ease in overweight and obese people: a modelling study. Lancet Diabetes Endocrinol. 2015; 3(2): 114–122, doi: 10.1016/S2213-8587(14)70229-3, indexed in Pubmed: 25483220.
37. Rodríguez-González GL, Reyes-Castro LA, Bautista CJ, et al. Maternal obesity accelerates rat offspring metabolic ageing in a sex-dependent manner. J Physiol. 2019; 597(23): 5549–5563, doi: 10.1113/JP278232, indexed in Pubmed: 31591717.
38. Stout MB, Justice JN, Nicklas BJ, et al. Physiological Aging: Links Among Adipose Tissue Dysfunction, Diabetes, and Frailty. Physiology (Bethesda). 2017; 32(1): 9–19, doi: 10.1152/physiol.00012.2016, indexed in Pubmed: 27927801.
39. Phillips MCl. Metabolic Strategies in Healthcare: A New Era. Aging Dis. 2022; 13(3): 655–672, doi: 10.14336/AD.2021.1018, indexed in Pubmed: 35656107.