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New approaches to treatment of metabolic syndrome — associated nephropathies: focus at lipid profile and adipokines

Alina A. Shevandova[1, 4], Leya E. Sorokina[1, 2], Irina I. Fomochkina[1], Anton V. Tkach[1], Andrey N. Glushenkov[3], Inna V. Chernousova[4], Mikhail E. Bychkov[1]

[1] Order of the Red Banner of Labor Medical Institute named after S.I. Georgievsky, Vernadsky Crimean Federal University, Simferopol, Russia
[2] National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov, Moscow, Russia
[3] Vernadsky Crimean Federal University, Physics and Technology Institute, Simferopol, Russia
[4] NRC "Kurchatov Institute" — "Magarach", Yalta, Russia

ABSTRACT

Background. Due to the increasing burden of metabolic diseases, the search for and development of pathogenetically sound and safe therapeutic strategies that influence the development and progression of nephropathy associated with metabolic syndrome is urgent.

Aim. To conduct a comparative evaluation of the effectiveness of various groups of drugs in correcting the metabolic profile and adipokine status to slow the progression of nephropathy associated with metabolic syndrome.

Materials and methods. An experimental study was conducted on Wistar rats. To simulate metabolic nephropathy, the animals were fed a solid diet containing 60% fructose. From weeks 14 to 24, the animals were administered various therapeutic compositions. At the end of the experiment, anthropometry of the animals was performed, and lipid metabolism parameters and blood adipokine levels were assessed.

Results. Results of multiple comparisons revealed no significant differences in cholesterol, triglyceride, high-density lipoprotein, low-density lipoprotein, or leptin and adiponectin levels between the groups of animals receiving corrective therapy and the metabolic syndrome group without correction. However, a positive effect on lipid status and adipokine parameters was observed with monotherapy with a dipeptidyl peptidase 4 inhibitor and grape seed concentrate.

Conclusions. The positive trends observed in normalizing adipose tissue metabolic activity with the dipeptidyl peptidase 4 inhibitor and grape seed concentrate indicate their potential in the combination therapy of nephropathies associated with metabolic syndrome. However, further clinical trials are required to confirm their efficacy and safety.

Keywords: metabolic syndrome, chronic kidney disease, polyphenol concentrates, nephroprotective therapy

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Новые подходы к терапии нефропатий, ассоциированных с метаболическим синдромом: фокус на липидный профиль и адипокины

А.А. Шевандова[1, 4], Л.Е. Сорокина[1, 2], И.И. Фомочкина[1], А.В. Ткач[1], А.Н. Глушенков[3], И.В. Черноусова[4], М.Э. Бычков[1]

[1] Ордена Трудового Красного Знамени Медицинский институт им. С.И. Георгиевского ФГАОУ ВО «КФУ им. В.И. Вернадского», г. Симферополь, Россия
[2] Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии им. В.И. Кулакова, г. Москва, Россия
[3] Физико-технический институт ФГАОУ ВО «КФУ им. В.И. Вернадского», г. Симферополь, Россия
[4] Курчатовский институт — «Магарач», г. Ялта, Россия

АННОТАЦИЯ

Актуальность. В связи с увеличением бремени метаболических заболеваний актуальным является поиск и разработка патогенетически обоснованных и безопасных терапевтических стратегий, влияющих на развитие и прогрессирование нефропатии, ассоциированной с метаболическим синдромом.

Цель — провести сравнительную оценку эффективности различных групп препаратов в коррекции метаболического профиля и адипокинового статуса для замедления прогрессирования нефропатии, ассоциированной с метаболическим синдромом.

Материалы и методы. Экспериментальное исследование проведено на крысах линии Wistar. Для моделирования метаболической нефропатии использовали модель кормления животных твердым кормом с 60% содержанием фруктозы. С 14-й по 24-ю неделю животным назначались различные терапевтические композиции. По завершении эксперимента были проведены антропометрия животных, оценка показателей липидного обмена и адипокинов в крови.

Результаты исследования. Результаты множественного сравнения не выявили достоверной разницы в уровне холестерина, триглицеридов, липопротеинов высокой и низкой плотности, а также в концентрациях лептина и адипонектина между группами животных, получающими коррекционную терапию, и группой метаболического синдрома без коррекции. Между тем отмечен положительный эффект в отношении показателей липидного статуса и адипокинов при монотерапии препаратом группы ингибиторов дипептидилпептидазы 4 и концентратами семян винограда.

Выводы. Выявленные позитивные тенденции к нормализации метаболической активности жировой ткани на фоне приема ингибитора дипептидилпептидазы 4 и концентрата семян винограда указывают на их потенциал в комплексной терапии нефропатий, связанных с метаболическим синдромом, однако для подтверждения их эффективности и безопасности требуются дальнейшие клинические испытания.

Ключевые слова: метаболический синдром, хроническая болезнь почек, полифенольные концентраты, нефропротективная терапия

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RELEVANCE

According to epidemiological studies, chronic kidney disease (CKD) is becoming more common. CKD is found in 13.4% people in the general population [10]. The high frequency of renal dysfunction is largely due to secondary nephropathies of dysmetabolic origin associated with metabolic syndrome (MS), obesity, hypertension, diabetes mellitus, and dyslipidemia. The dominant role of MS in the growth of worldwide CKD prevalence has been established. Metabolically induced nephropathy is detected in a significant proportion of patients with CKD, ranging from 20 to 50% depending on the region and population studied [12]. The presence of MS increases the risk of developing nephropathy on average 2.6 times. In patients with two, three, four, or five MS criteria, the likelihood of developing CKD increases by 2.21, 3.38, 4.23, and 5.85 times higher, respectively, compared to patients who do not have any or only one criterion for the syndrome. With a duration of MS of nine years or more, the risk of developing CKD increases by approximately 50% [13].

The most significant mechanisms contributing to the development and progression of chronic kidney disease (CKD) in metabolic syndrome (MS) are associated with excessive accumulation of adipose tissue, the development of chronic low-intensity inflammation, oxidative stress, and insulin resistance (IR). Adipose tissue dysfunction contributes to the formation of cardiometabolic risk factors and the development of CKD. Over time, these interrelated pathological processes lead to a gradual decline in kidney function, increasing the risk of cardiovascular disease, renal failure, disability, and death.

In this regard, it is important to search for and develop pathogenetically sound and safe therapeutic strategies that influence the development and progression of metabolically induced nephropathy. The possibility of preventing the progression of CKD in patients with MS and elevated blood pressure (BP) is determined by the timely use of antihypertensive therapy. To reduce proteinuria, the use of drugs that suppress the renin-angiotensin-aldosterone system (RAAS) is recommended. The nephroprotective properties of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) have been proven [9].

Currently, the use of hypoglycemic drugs from the group of dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists are being studied in slowing the progression of CKD. In addition to glycemic control, drugs from these groups exhibit nephroprotective properties, reducing inflammation and improving endothelial function [2, 4, 7].

Another promising therapeutic approach is the use of polyphenolic concentrates to target common key pathogenetic mechanisms characteristic of CKD and MS. With their anti-inflammatory and antioxidant activity, polyphenols can exert an angioprotective effect and improve cell sensitivity to insulin [8, 15].

AIM

The aim of the study is to conduct a comparative assessment of various groups of drugs in correcting the metabolic profile and adipokine status to slow the progression of nephropathy associated with metabolic syndrome.

MATERIALS AND METHODS

The experimental study was performed on male Wistar rats (age 2.5–3 months, weight 250–300 g (initially) obtained from the SMK STEZAR breeding facility (Russian Federation). MS and associated kidney damage in rats were modeled using a fructose feeding model: standard solid feed “Combifood LBC-120”[1] with 60% fructose added. The initial duration of MS modeling was 14 weeks. The animals in the control group were fed standardized diet without fructose. The animals were then divided into groups depending on the drug they received for 10 weeks:

- Group 1: control group — intact animals (n=5);
- Group 2: MS without correction (n=6);
- Group 3: MS with BRA II inhibitor GScorrection — azilsartan medoxomil (Heopharm, Russia) (n=8);
- Group 4: MS with correction with sodium-glucose cotransporter 2 (SGLT2) inhibitors — ipragliflozin (Astellas Pharma, Japan) (n=8);
- Group 5: MS with correction using dipeptidyl peptidase-4 (DPP-4) inhibitors — gozogliptin (Pharmsintez-Tyumen, Russia) (n=6);
- Group 6: MS with correction using non-alcoholic grapevine concentrate (GVC) (Kurchatov Institute — Magarach, Yalta, Russia) (n=10);
- Group 7: MS with correction using non-alcoholic grape seed concentrate (GSC) (Kurchatov Institute — Magarach, Yalta, Russia) (n=8);
- Group 8: MS with correction using a combination of azilsartan medoxomil and GVC (n=11).

The experiment lasted for 24 weeks.

At the end of the study, after a 12-hour fasting period, euthanasia was performed by decapitation under inhalation anesthesia with the veterinary drug Isoflurane (MIRALEK-AGRO LLC, Russian Federation). The study complied with regulatory requirements established by the European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes; and a positive opinion was obtained from the local bioethics committee of the Federal State Autonomous Educational Institution of Higher Education “V.I. Vernadsky KFU”, protocol No. 7 dated 25.06.2024.

[1] GOST 23462-2019. Products of the compound feed industry. Acceptance rules, packaging, labeling, transportation, and storage.

Blood serum was obtained by centrifuging whole blood from animals for 15 minutes at 3000 rpm. Lipid profile parameters, including total cholesterol (TC), triglycerides (TG), high-density lipoproteins (HDL) and low-density lipoproteins (LDL), were assessed using an Express Plus automatic biochemical analyzer (Bayer Diagnostics, Germany). Serum levels of leptin and adiponectin were determined by solid-phase enzyme-linked immunosorbent assay (ELISA) using specialized kits (Cloud-Clone, China) on a Multiskan FC analyzer (Thermo Fisher Scientific, Finland).

Statistical analysis was performed in R (version 4.3.3) (R Core Team, 2024) using the WRS package (version 0.44). Given the small sample size in the study groups, the 20% truncated mean was used as a descriptive statistic. This measure ensures the stability of the results against deviations from normal distribution (asymmetry and heavy tails), while maintaining an interpretation similar to the standard mean.

Paired comparisons of the control group and the experimental group with reproduced MS without correction were performed graphically: by plotting a shift function graph. Differences were considered statistically significant when partial or complete stochastic inequality was observed.

A one-factor Welch-like test for 20% truncated means was used for multiple group comparisons. Type I error control of p-values was performed using the Homel method. A post-hoc set of pairwise comparisons was performed by comparing linear contrasts for 20% truncated means.

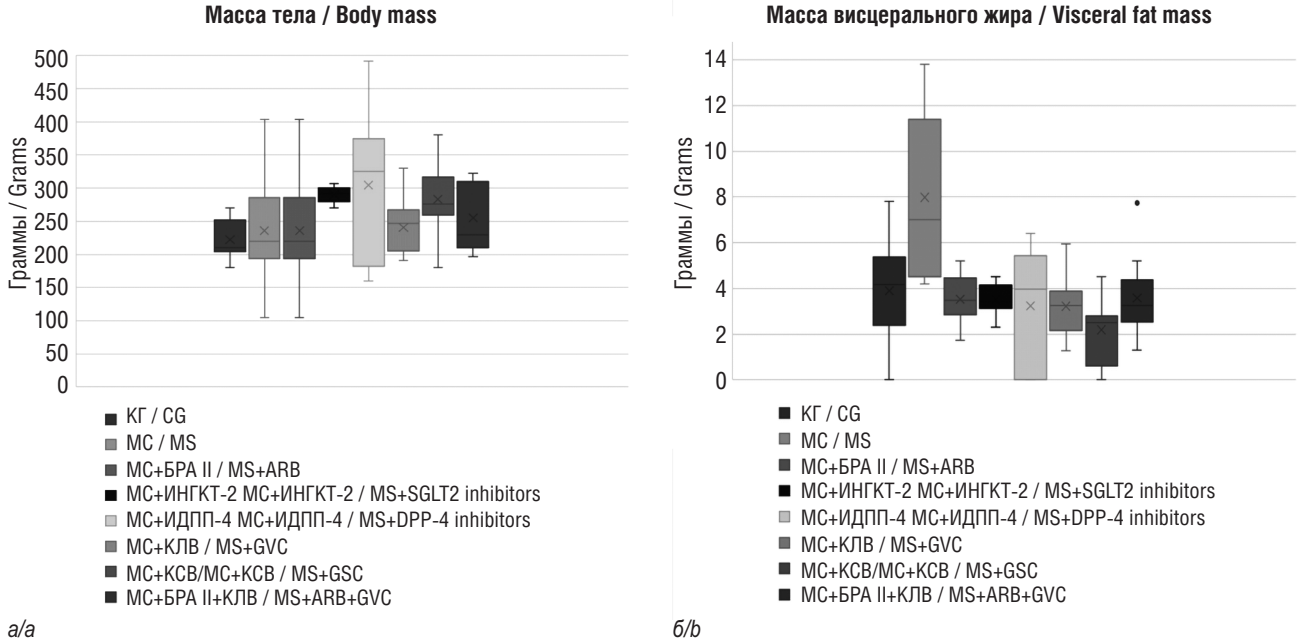
The effect size was estimated by calculating the standardized difference δ-value of KMS (Kulinsky–Morgensthaler–Staudt) for the 20% truncated mean, where 0.2 corresponded to a small effect, 0.5 corresponded to a medium effect size, and 0.8 corresponded to a large effect size, as well as explanatory power (ξ): ξ=0.15 corresponded to a weak effect size, 0.35 corresponded to a medium effect size, and 0.5 corresponded to a strong effect size. In this study, p-values were considered as an indicator of study quality.

RESULTS

The development of metabolic syndrome and associated kidney damage was accompanied by lipid metabolism disorders, manifested by weight gain, visceral fat accumulation, and dyslipidemia. In the uncorrected MS group, there was a stochastic increase in body weight, total cholesterol, triglycerides, low-density lipoproteins, and a decrease in high-density lipoprotein concentration compared to the control group. The results of multiple group comparisons revealed differences in cholesterol (ξ=0.51, p=0.220891), triglycerides (ξ=0.44, p=0.121865), LDL (ξ=0.39, p=0.192091), and HDL (ξ=0.76, p=0.041332), as well as in body weight (ξ=0.75, p=0.000140) and abdominal fat (ξ=0.53, p=0.031278) in the MS group without correction and against the background of taking the studied drugs (Fig. 1, Tables 1, 2).

A graph of the shift function of leptin and adiponectin indicators revealed partial stochastic inequality in the control and MS groups without correction.

The results of multiple comparisons of groups in terms of markers of renal damage revealed a difference in the levels of leptin (ξ=0.39, p=0.921722) and adiponectin (ξ=0.57, p=0.000704) in the MS group without correction and against the background of taking the studied drugs.



а/a *б/b*

Fig. 1. Body weight of animals (*a*) and the amount of visceral fat (*b*) in the analyzed groups of animals

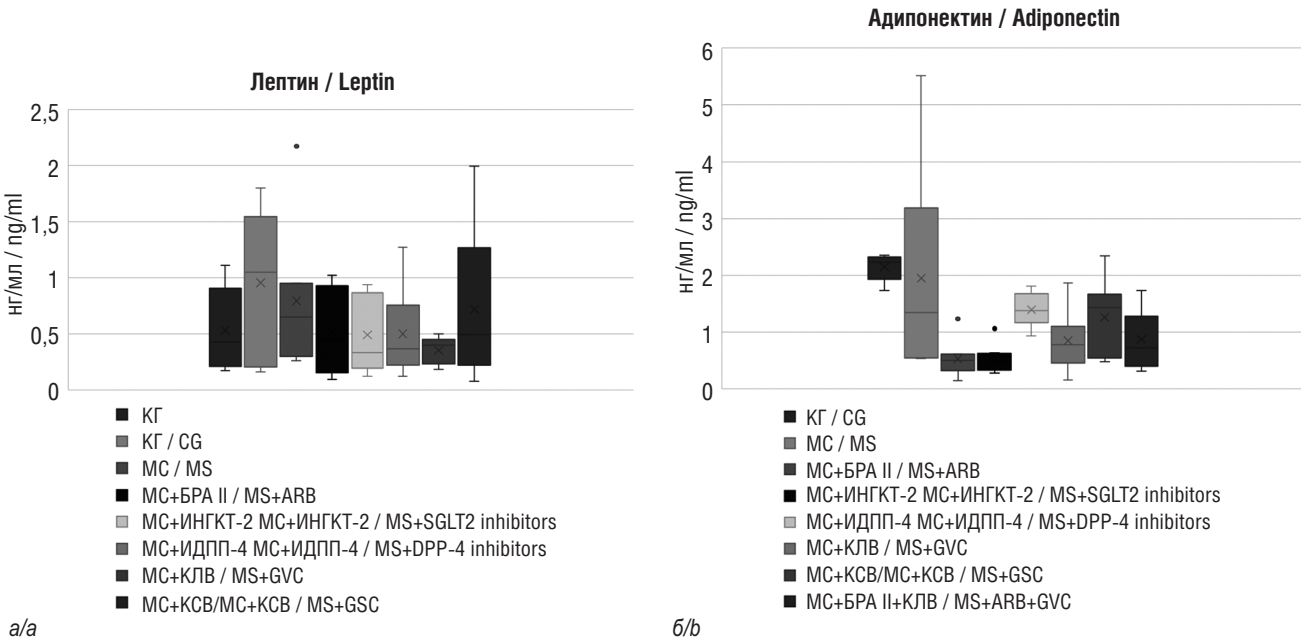
Рис. 1. Масса тела животных (*а*) и количество висцерального жира (*б*) в анализируемых группах животных

Table 1. Effect sizes and difference in position measures (20% trimmed mean) of the intervention groups compared to the untreated metabolic syndrome group for body weight and visceral fat

Таблица 1. Показатели уровня эффекта и разность мер положения (20%-усеченное среднее) групп, получающих коррекционную терапию, по сравнению с группой метаболического синдрома без коррекции, в отношении массы тела и висцерального жира

Группы животных / Animal groups	Масса тела / Body mass	Масса висцерального жира / Visceral fat mass
МС + БРА II / MS + ARB II	Сильный / Strong (ξ=0,92), 167,286 (95% ДИ / CI: 70,359; 264,212, p_{Adj} = 0,000845)	Сильный / Strong (ξ=0,72), –4,157 (95% ДИ / CI: –11,033; 2.71, p_{Adj}= 0,350371)
МС + ИНГКТ-2 / MS + SGLT2 inhibitors	Сильный / Strong (ξ=0,76), 60,619 (95% ДИ / CI: –28,209; 149,447, p_{Adj}=0,238442)	Сильный / Strong (ξ=0,75), –4,146 (95% ДИ / CI: –11,065; 2,772, p_{Adj}=0,343269)
МС + ИДПП-4 / MS + DPP-4 inhibitors	Средний / Average (ξ=0,46), 64,286 (95% ДИ / CI: –209,440; 338,011, p_{Adj}=0,946789)	Сильный / Strong (ξ=0,82), –3,671 (95% ДИ / CI: –10,556; 3,213, p_{Adj}=0,52937)
МС + КЛВ / MS + GVC	Отсутствует / No (ξ=0,09), 8,386 (95% ДИ/ CI: –80,514; 97,285, p_{Adj}=0,999999)	Сильный / Strong (ξ=0,74), –4,620 (95% ДИ / CI: –11,507; 2,267, p_{Adj}=0,251003)
МС + КСВ / MS + GSC	Сильный / Strong (ξ=0,57), 53,119 (95% ДИ / CI: –35,441; 141,679, p_{Adj}= 0,412475)	Сильный/ Strong (ξ=0.82), –4.921 (95% ДИ / CI: –11.866; 2.024, p_{Adj}= 0.198632)
МС + БРА II + БКЛВ / MS + ARB + GVC	Слабый / Weak (ξ=0,21), 21,714 (95% ДИ / CI: –91,706; 135,135, p_{Adj}= 0,999961)	Сильный / Strong (ξ=0,71), –4,396 (95% ДИ / CI: –11,270; 2,477, p_{Adj}=p=0,296869)

Notes: CI — confidence interval.
Примечания: ДИ — доверительный интервал.



а/a *б/b*

Fig. 2. Levels of leptin (*a*) and adiponectin (*b*) in the blood serum of animals of the analyzed groups

Рис. 2. Уровни лептина (*а*) и адипонектина (*б*) в сыворотке крови животных анализируемых групп

Figure 2 shows the range of the markers studied, and the effect size for each corrective drug is presented in Table 3.

DISCUSSION

The central link in cardiovascular-renal-metabolic disorders is visceral obesity, which is considered a powerful risk factor for the development of secondary IR. Compensatory hyperinsulinemia, which inevitably develops against the background of IR, leads to ectopic accumulation of adipose tissue, closing the vicious circle and causing a whole range of other pathophysiological complications, including arterial hypertension, dyslipidemia, and atherosclerosis [1].

At the same time, there is a growing body of evidence suggesting that kidney involvement may occur independently in the presence of obesity, even in the absence of hypertension and/or diabetes mellitus. The direct role of

Table 2. Lipid profile of animals of the analyzed groups

Таблица 2. Липидный профиль животных анализируемых групп

Группы животных / Animal groups	ОХ, ммоль/л / TC, mmol/l	ТГ, ммоль/л / TG, mmol/l	ЛПНП, ммоль/л / LDL, mmol/l	ЛПВП, ммоль/л / HDL, mmol/l
КГ / CG	1,008	0,651	0,2042	0,476
МС / MS	1,011*	0,666*	0,291*	0,436*
МС + БРА II / MS + ARB	1,16 (ξ=0,32)** 0,148 (95% ДИ / CI: –0,497; 0,794, p_{Adj}= 0,997813)	0,546 (ξ=0,43)** –0,119 (95% ДИ / CI: –0,427; 0,189, p_{Adj}= 0,880866)	0,342 (ξ=0,44)** 0,050 (95% ДИ / CI: –0,085; 0,185, p_{Adj}=0,929548)	0,758 (ξ=0,77)** 0,323 (95% ДИ / CI: –0,024; 0,669, p_{Adj}=0,075692)
МС + ИНГКТ-2 / MS + SGLT2 inhibitors	1,268 (ξ=0,42)** 0,257 (95% ДИ / CI: –0,395; 0,909, p_{Adj}=0,878793)	0,683 (ξ=0,11)** 0,018 (95% ДИ / CI: –0,295; 0,331, p_{Adj}=1,000000)	0,328 (ξ=0,35)** 0,037 (95% ДИ / CI: –0,120; 0,194, p_{Adj}=0,999170)	0,652 (ξ=0,92)** 0,216 (95% ДИ / CI: –0,053; 0,485, p_{Adj}=0,141381)
МС + ИДПП-4 / MS + DPP-4 inhibitors	1,107 (ξ=0,28)** 0,096 (95% ДИ / CI: –0,558; 0,750, p_{Adj}=0,999993)	0,53 (ξ=0,37)** –0,136 (95% ДИ / CI: –0,476; 0,205, p_{Adj}=0,869150)	0,270 (ξ=0,22)** –0,021 (95% ДИ / CI: –0,179; 0,136, p_{Adj}=0,999998)	0,552 (ξ=0,59)** 0,117 (95% ДИ / CI: –0,170; 0,404, p_{Adj}= 0,852784)
МС + КЛВ / MS + GVC	1.433 (ξ=0.61)** 0.421 (95%-ДИ / CI: –0.236; 1.079, p_{Adj}=0.391284)	0,629 (ξ=0,15)** –0,037 (95% ДИ / CI: –0,343; 0,270, p_{Adj}=0,999999)	0,336 (ξ=0,26)** 0,044 (95% ДИ / CI: –0,126; 0,215, p_{Adj}=0,999086)	0.708 (ξ=0,85)** 0,272 (95% ДИ / CI: –0,034; 0,579, p_{Adj}=0,104932)
МС + КСВ / MS + GSC	1.258 (ξ=0.38)** 0.247 (95% ДИ / CI: –0.486; 0.979, p_{Adj}=0.971319)	0,66 (ξ=0,05)** –0,006 (95% ДИ / CI: –0,314; 0,302, p_{Adj}=1,000000)	0,265 (ξ=0,18)** –0,026 (95% ДИ / CI: –0,160; 0,107, p_{Adj}=0,999844)	0,6 (ξ=0,78)** 0,164 (95% ДИ / CI: –0,114; 0,442, p_{Adj}=0,470810)
МС + БРА II + БКЛВ / MS + ARB + GVC	1,118 (ξ=0,15)** 0,107 (95% ДИ / CI: –0,588; 0,802, p_{Adj}=0,999998)	0,54 (ξ=0,26)** –0,126 (95%-ДИ / CI: –0,442; 0,190, p_{Adj}=0,896545)	0,334 (ξ=0,29)** 0,043 (95% ДИ / CI: –0,143; 0,228, p_{Adj}=0,999383)	0,661 (ξ=0,75)** 0,226 (95% ДИ / CI: –0,063; 0,514, p_{Adj}=0,185682)

Notes: * — compared to the control group; ** — compared to the MS group without correction; CI — confidence interval.
Примечания: * — по сравнению с группой контроля; ** — по сравнению с группой МС без коррекции; ДИ — доверительный интервал.

adipose tissue dysfunction in the development and progression of nephropathies has been proven [14]. Thus, the negative effect of visceral obesity on the kidneys may be a consequence of developing comorbid conditions, such as diabetes mellitus, hypertension. It can also result from the direct impact of adipose tissue on the kidneys associated with the endocrine activity of substances produced by adipocytes (leptin, adiponectin, etc.) [20]. Recent studies confirm a close relationship between adipokines and CKD, especially in the presence of metabolic disorders [16]. The results of our experimental study confirm these data. The results obtained in this study reflect a significant increase in visceral fat mass, lipid profile disorders, an increase in leptin concentration, and a decrease in serum adiponectin concentration when renal disorders are associated with MS.

The multicomponent nature of the pathogenesis of dysmetabolic nephropathy suggests that therapy aimed at reducing visceral fat mass and normalizing the levels of biologically active substances involved in the regulation of fat metabolism may slow the progression of the disease. In the course of the current study, a comparative assessment was made to evaluate efficacy of BRA II drugs with potent antihypertensive potential, innovative drugs SGTL-2 and DPP-4 inhibitors with claimed hypoglycemic effects, as well as plant polyphenolic concentrates with antioxidant and anti-inflammatory properties.

A trend toward weight loss, mainly due to visceral adipose tissue, was observed in all groups of animals with MS receiving corrective therapy. Given that visceral adipose tissue is more sensitive to catecholamine-dependent lipolysis and less sensitive to the antilipolytic action of insulin, further studies of the indirect effects of the drugs under investigation on the sympathoadrenal system are needed to explain the observed reduction in visceral fat mass.

At the same time, the drugs under study did not have the expected effect on the metabolic activity of adipose

Table 3. Trimmed mean difference (20%) and comparative assessment of leptin and adiponectin levels in animals with metabolic syndrome: treatment groups versus uncorrected group

Таблица 3. Разность усеченных средних (20%) и сравнительная оценка уровней лептина и адипонектина у животных с метаболическим синдромом: терапевтические группы по сравнению с группой без коррекции

Группы животных / Animal groups	Лептин, нг/мл / Leptin, ng/ml	Адипонектин, нг/мл / Adiponectin, ng/ml
МС + БРА II / MS + ARB	Слабый / Weak (ξ=0,29), –0,319 (95% ДИ / CI: –2,506; 1,867, p_{Adj}=0,998800)	Сильный / Strong (ξ=0,76), –0,934 (95% ДИ / CI: –4,635; 2,766, p_{Adj}=0,806773)
МС + ИНГКТ-2 / MS + + SGLT2 inhibitors	Средний / Average (ξ=0,43), –0,437 (95% ДИ / CI: –2,586; 1,712, p_{Adj}=0,984903)	Сильный / Strong (ξ=0,76), –0,931 (95% ДИ / CI: –4,632; 2.770, p_{Adj}=0,809205)
МС + ИДПП-4 / MS + + DPP-4 inhibitors	Средний / Average (ξ=0,49), –0,479 (95% ДИ / CI: –2,683; 1,725, p_{Adj}=0,982090)	Отсутствует / No (ξ=0,006), –0,006 (95% ДИ / CI: –3,608; 3,597, p_{Adj}=1,000000)
МС + КЛВ / MS + GVC	Отсутствует / No (ξ=0,13), –0,249 (95% ДИ / CI: –2,701; 2,202, p_{Adj}= 0,999998)	Отсутствует / No (ξ=0,09), –0,194 (95% ДИ / CI: –3,456; 3,067, p_{Adj}=1,000000)
МС + КСВ / MS + GSC	Средний / Average (ξ=0,47), –0,500 (95% ДИ / CI: –2,742; 1,742, p_{Adj}=0,944771)	Средний / Average (ξ=0,5), –0,631 (95% ДИ / CI: –4,243; 2,981, p_{Adj}=0,972475)
МС + БРА II + БКЛВ / MS + ARB + GVC	Слабый / Weak (ξ=0,29), –0,314 (95% ДИ / CI: –2,395; 1,767, p_{Adj}=0,999727)	Сильный / Strong (ξ=0,54), –0,662 (95% ДИ / CI: –4,183; 2.858, p_{Adj}=0,967647)

Notes: CI — confidence interval.
Примечания: ДИ — доверительный интервал.

tissue. According to available scientific reports, BRA II, SGTL-2, DPP-4 inhibitors and polyphenolic compounds groups are capable of exerting positive pleiotropic effects on the lipid profile and adipokines in individuals with metabolic and cardiovascular disorders [2, 7]. However, the above-mentioned literature data are still contradictory and have not been reliably confirmed in our experimental study. Apparently, the noted dissonance is due to a number of objective reasons, as well as the pharmacodynamic characteristics of the drugs themselves.

The lack of clear conclusions regarding how the groups of drugs studied affect the metabolic activity of adipose tissue can be explained by a small sample size, varying degrees of severity of the subjects' conditions, and individual differences in metabolism. Moreover, it should be noted that in a number of previous clinical studies in patients with endocrinological and cardiological profiles, combination therapy was used, and assessing the lipid profile was not always a primary endpoint.

As for the potential effects of BRA II inhibitors, it's been suggested that these drugs have a dose-dependent effect on lipid metabolism [9]. In addition, several studies have described the phenomenon of partial escape from angiotensin II blockade in patients with type 2 diabetes mellitus and diabetic nephropathy, which may also apply to the results of our study [3, 11].

The lack of effect on lipid profile and adipokine levels when taking ipragliflozin in animals with nephropathy against the background of MS, is, in our opinion, associated with an increase in LDL concentration due to hemoconcentration caused by natriuresis and a decrease in the expression of LDL receptors on the surface of hepatocytes. SGLT2 inhibitors "switch" energy metabolism to lipid utilization, moderately increasing ketone production and intracellular cholesterol synthesis, and also reduces cholesterol absorption in the intestine [5].

At the same time, it is important to note the positive trend toward normalization of TG, LDL, VLDL, and leptin levels in groups of animals with MS and nephropathy that received IDPP-4 and GSC drugs.

The effect of gozogliptin on blood lipid and adipokine levels has not been sufficiently studied. However, it has been reported that, in addition to their declared hypoglycemic effect, IDPP-4 drugs are capable of directly and indirectly regulating lipid metabolism. An in vitro experiment has shown that the hypolipidemic effect of DPP-4 inhibitors may be associated with a decrease in cholesterol synthesis in the liver and an increase in lipoprotein catabolism, occurring against the background of increased insulin secretion and enhanced tissue sensitivity to insulin [4]. In addition, there are increasing suggestions that other tissues, including the intestine, are involved in the hypolipidemic effect of IDPP-4. In another study using DNA microarray technology, the authors show that IDPP-4 affects plasma triglyceride and cholesterol levels through its inhibitory activity on the transcription factor SREBP2 (Sterol Regulatory Element-Binding Protein 2, a protein that binds to the sterol regulatory element 2), the main regulator of cholesterol and lipid homeostasis [19].

Currently, there is widespread discussion regarding the potential of polyphenols as promising biologically active compounds in treating and preventing obesity against a backdrop of metabolic disorders. The accumulated data indicate that polyphenols can reduce preadipocyte proliferation, suppress adipocyte differentiation and viability, and have a normalizing effect on the metabolic activity of adipose tissue [15]. Meanwhile, these pleiotropic effects are the prerogative of certain subtypes of flavonoids, in-

cluding catechins and quercetin [6]. The effect of these compounds is determined by their interaction with cell membranes, changing the phase state of membrane lipids and their structural organization. The literature reports indicate that polyphenols influence the expression of nuclear and cytoplasmic proteins. Their participation in cell signaling systems, in particular mTOR (mechanistic Target of Rapamycin), appears to be an important component of the physiological activity of bioflavonoids. Suppression of mTOR activity prevents adipogenesis and disrupts the viability of adipocytes, while its excessive activation promotes adipogenesis [18]. Activation of AMP-dependent protein kinase gene expression indicates the involvement of LKB1/AMPK (Liver Kinase B1/AMP-activated Protein Kinase), a signaling pathway in polyphénol concentrate action. The suppression of lipid synthesis is caused by a decrease in the activity of acetyl-CoA carboxylase, and the stimulation of β-oxidation is caused by the activation of carnitine palmitoyltransferase I and mitochondrial uncoupling protein UCP2 through receptors activated by peroxisome proliferator-activated receptors (PPAR) α [17].

It is important to note that the flavonoid compounds described are present in significantly higher amounts in grape seed concentrate than in vine concentrates, which directly explains a more pronounced hypolipidemic effect in the group of animals with metabolic nephropathy that received GSC. Despite the high content of resveratrol in GVC, which has powerful anti-inflammatory and antioxidant activity, the total content of water-soluble antioxidants was significantly higher in grape seed concentrate, which also likely played a significant role in reducing the intensity of oxidative stress associated with excess adipose tissue and allowed for the normalization of adipose tissue metabolic activity.

Given the lack of a pronounced positive effect on lipid status and adipokine levels with monotherapy with BRAII inhobitors and GSC, their combined use also did not demonstrate the expected effect on existing adipose tissue dysfunction in animals with nephropathy against the background of MS.

CONCLUSION

1. A comparative assessment of the efficacy of drugs from the BRA II, SGLT-2, and DPP-4 inhibitor groups, as well as plant polyphenol concentrates, revealed a positive effect on body weight reduction, mainly due to visceral fat mass in animals with metabolically induced nephropathy.

2. The studied drugs did not have a pronounced effect on lipid profile and adipokine indicators in nephropathy associated with MS.

3. The identified positive trends towards normalization of adipose tissue metabolic activity against the background of IDPP-4 and GSC administration give these therapeutic agents a reputation as promising means of metabolic control in the complex therapy of the most complex group of patients with MS and nephropathy. However, further research is needed to confirm the efficacy and safety of these therapeutic compositions.

ADDITIONAL INFORMATION

Author contribution. All authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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AUTHORS' INFO

Alina A. Shevandova, Junior Researcher, Assistant of the Department of Basic and Clinical Pharmacology, Order of the Red Banner of Labor Medical Institute named after S.I. Georgievsky, Federal State Autonomous Educational Institution of Higher Education "Vernadsky Crimean Federal University", Simferopol, Russia; Junior Researcher, Laboratory of analytical research, innovative and resource-saving technologies, NRC "Kurchatov Institute" — "Magarach", Yalta, Russia;
ORCID: 0000-0002-9448-6034; eLibrary SPIN: 6199-4876;
e-mail: shevandova_a_a@mail.ru

*** Leya E. Sorokina**, Junior Researcher, Central Research Laboratory, Order of the Red Banner of Labor Medical
Institute named after S.I. Georgievsky, Federal State Autonomous Educational Institution of Higher Education "Vernadsky Crimean Federal University"; address: 5/7 Lenina blvd., Simferopol, 295051, Russia; Junior Researcher, Laboratory of cytology, FSBI "National Medical Research Center for Obstetrics, Gynecology and Perinatology named after Academician V.I. Kulakov"; address: 4, Oparina str., Moscow, 117997, Russia;
ORCID: 0000-0002-1862-6816; eLibrary SPIN: 5934-0679;
e-mail: leya.sorokina@mail.ru

ОБ АВТОРАХ

Алина Алексеевна Шевандова, ассистент кафедры базисной и клинической фармакологии Ордена Трудового Красного Знамени Медицинский институт им. С.И. Георгиевского, ФГАОУ ВО «КФУ им. В.И. Вернадского», г. Симферополь, Россия; младший научный сотрудник лаборатории аналитических исследований, инновационных и ресурсосберегающих технологий НИЦ «Курчатовский институт» — «Магарач», г. Ялта, Россия; ORCID: 0000-0002-9448-6034; eLibrary SPIN: 6199-4876; e-mail: shevandova_a_a@mail.ru

*** Лея Евгеньевна Сорокина**, младший научный сотрудник, Центральная научно-исследовательская лаборатория, Ордена Трудового Красного Знамени Медицинский институт им. С.И. Георгиевского, ФГАОУ ВО «КФУ им. В.И. Вернадского»; адрес: Россия, 295051, г. Симферополь, бульвар Ленина, д. 5/7; младший научный сотрудник ФГБУ «Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии им. В.И. Кулакова», адрес: Россия, 117997, Москва, ул. Академика Опарина, д. 4;
ORCID: 0000-0002-1862-6816; eLibrary SPIN: 5934-0679;
e-mail: leya.sorokina@mail.ru

AUTHORS' INFO

Irina I. Fomochkina, MD, PhD, Dr. Sci. (Med.), Professor, Deputy Director for Scientific and Innovative Activities, Head of the Department of Basic and Clinical Pharmacology, Order of the Red Banner of Labor Medical Institute named after S.I. Georgievsky, Federal State Autonomous Educational Institution of Higher Education "Vernadsky Crimean Federal University", Simferopol, Russia; ORCID: 0000-0003-3065-5748; eLibrary SPIN: 3281-4940; e-mail: fomochkina_i@mail.ru

Anton V. Tkach, Junior Researcher, Department of Basic and Clinical Pharmacology, Order of the Red Banner of Labor Medical Institute named after S.I. Georgievsky, Federal State Autonomous Educational Institution of Higher Education "Vernadsky Crimean Federal University", Simferopol, Russia; ORCID: 0000-0002-9234-3021; eLibrary SPIN: 6275-7792; e-mail: v_veber00@mail.ru

Andrey N. Glushenkov, Senior Lecturer, Department of Condensed Matter, Physical Methods and Information Technologies in Medicine, Physics and Technology Institute, Federal State Autonomous Educational Institution of Higher Education "Vernadsky Crimean Federal University", Simferopol, Russia; ORCID: 0000-0003-1704-6083; eLibrary SPIN: 4221-6613; e-mail: an.glushenkov@yandex.ru

Inna V. Chernousova, PhD in Engineering, Leading Researcher, Laboratory of Functional Products of Grape Processing, NRC "Kurchatov Institute" — "Magarach", Yalta, Russia; ORCID: 0000-0001-5374-7683; eLibrary SPIN: 5079-7416; e-mail: cherninna1@mail.ru

Mikhail E. Bychkov, 5th year student, Department of Basic and Clinical Pharmacology, Order of the Red Banner of Labor Medical Institute named after S.I. Georgievsky, Federal State Autonomous Educational Institution of Higher Education "Vernadsky Crimean Federal University", Simferopol, Russia; ORCID: 0009-0008-1854-0917; eLibrary SPIN: 5821-7151; e-mail: exitet2015@mail.ru

ОБ АВТОРАХ

Ирина Ивановна Фомочкина, д-р мед. наук, профессор, заместитель директора по научной и инновационной деятельности, заведующая кафедрой базисной и клинической фармакологии, Ордена Трудового Красного Знамени Медицинский институт им. С.И. Георгиевского, ФГАОУ ВО «КФУ им. В.И. Вернадского», г. Симферополь, Россия; ORCID: 0000-0003-3065-5748; eLibrary SPIN: 3281-4940; e-mail: fomochkina_i@mail.ru

Антон Владиславович Ткач, младший научный сотрудник, кафедра базисной и клинической фармакологии, Ордена Трудового Красного Знамени Медицинский институт им. С.И. Георгиевского, ФГАОУ ВО «КФУ им. В.И. Вернадского», г. Симферополь, Россия; ORCID: 0000-0002-9234-3021; eLibrary SPIN: 6275-7792; e-mail: v_veber00@mail.ru

Андрей Николаевич Глушенков, старший преподаватель кафедры физики конденсированных сред, физических методов и информационных технологий в медицине, Физико-технический институт, ФГАОУ ВО «КФУ им. В.И. Вернадского», г. Симферополь, Россия; ORCID: 0000-0003-1704-6083; eLibrary SPIN: 4221-6613; e-mail: an.glushenkov@yandex.ru

Инна Владимировна Черноусова, канд. тех. наук, ведущий научный сотрудник, лаборатория функциональных продуктов переработки винограда, НИЦ «Курчатовский институт» — «Магарач», г. Ялта, Россия; ORCID: 0000-0001-5374-7683; eLibrary SPIN: 5079-7416; e-mail: cherninna1@mail.ru

Михаил Эдуардович Бычков, студент 5-го курса 1-го медицинского факультета, Ордена Трудового Красного Знамени Медицинский институт им. С.И. Георгиевского, ФГАОУ ВО «КФУ им. В.И. Вернадского», г. Симферополь, Россия; ORCID: 0009-0008-1854-0917; eLibrary SPIN: 5821-7151; e-mail: exitet2015@mail.ru

* Автор, ответственный за переписку / Corresponding author.