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# NEW APPROACHES TO ENDOCRINOPATHY IN CARDIOVASCULAR DISEASES WITH METABOLIC SYNDROME

Mirzaeva A. Kh.
Alfraganus University, Tashkent

**Abstract**:

Epidemiologic data from observational studies and clinical trials provide substantial evidence of significant overlap between metabolic and cardiovascular diseases. Recognizing this complex relationship, the American Heart Association (AHA) recently introduced the concept of a combined disease known as cardiovascular and metabolic syndrome (CKM), emphasizing the close association and interaction between these areas of health. The purpose of this study is to provide a comprehensive and critical analysis of the current state of play regarding the newly defined CKM syndrome. This includes an examination of the epidemiologic and experimental data establishing links between cardio-metabolic diseases, an exploration of the underlying pathophysiological mechanisms and a comprehensive review of existing treatments.

**Keywords**: CKM; Cardiovascular metabolic syndrome; Metabolic syndrome; Obesity; American Heart Association (AHA); Hepatoprotector; Gossypol derivative.

**Introduction**

# НОВЫЕ ПОДХОДЫ ЭНДОКРИНОПАТИИ ПРИ СЕРДЕЧНО-СОСДИСТЫХ ЗАБОЛЕВАНИИ С МЕТАБОЛИЧЕСКОМ СИНДРОМОМ

Мирзаева А. Х.
Alfraganus University, Ташкент
+998997833755

Эпидемиологические данные наблюдательных исследований и клинических испытаний предоставляют существенные доказательства значительного совпадения между метаболическими, сердечно-сосудистыми заболеваниями. Признавая эту сложную взаимосвязь, Американская кардиологическая ассоциация (AHA) недавно представила концепцию комбинированного заболевания, известного как сердечно-сосудистый и метаболический синдром (CKM), подчеркивая тесную связь и

взаимодействие между этими областями здоровья. Целью данного исследования является предоставление всестороннего и критического анализа текущего состояния дел в отношении недавно определенного синдрома СКМ. Это включает в себя исследование эпидемиологических и экспериментальных данных, устанавливающих связи между кардио-метаболическими заболеваниями, изучение основных патофизиологических механизмов и всесторонний обзор существующих методов лечения.

**Ключевые слова:** СКМ; Сердечно-сосудистый метаболический синдром; метаболический синдром; Ожирение; Американская кардиологическая ассоциация (AHA) гепатопротектор; производное госсипола

## METABOLIK SINDROM BILAN YONDOSH KELUVCHI YURAK-QON TOMIR KASALLIKLARIDA ENDOKRINOPATIYAGA YANGI YONDASHUVLAR

Mirzayeva A.X.
Alfraganus University, Tashkent

Klinik tadqiqotlardan olingan epidemiologik ma'lumotlarga asosan metabolik va yurak-qon tomir kasalliklari o'rtasidagi boglanish borligini asoslaydi. Ushbu murakkab munosabatlarni Amerika yurak assotsiatsiyasi (AHA) yaqinda yurak-qon tomir va metabolik sindrom (YuQTMS) deb nomlanuvchi qo'shma kasallik kontseptsiyasini taqdim etdi va bu ushbu sohalari o'rtasidagi yaqin aloqalar tahlil qilindi. Ushbu tadqiqotning maqsadi yangi aniqlangan YuQTMS sindromi bilan bog'liq mexanizmlarni har tomonlama va tanqidiy tahlil qilishdir. Bu kardiometabolik kasalliklar o'rtasidagi bog’liqlikni epidemiologik va eksperimental ma'lumotlarga asoslanib tekshirish, asosiy patofiziologik mexanizmlarni o’rganish va mavjud davolash usullarini har tomonlama ko'rib chiqishni o'z ichiga oladi.

**Kalit so'zlar:** YuQTMS; Yurak-qon tomir metabolik sindromi; metabolik sindrom; Semizlik; Amerika yurak assotsiatsiyasi (AHA) gepatoprotektor; gossipol hosilasi

## Background

According to extensive data, cardiovascular disease (CVD) and metabolic syndrome (MS) are major health problems associated with significant morbidity and mortality. These conditions are believed to frequently coexist [1]. Cardiovascular disease (CVD) is often a complication of MS. According to the National Health and Nutrition Examination Survey (NHANES) dataset from 2017 to March 2020, the prevalence of CVD, including congenital heart defects, heart failure (HF), stroke, and hypertension, among adults aged 20 years and older was 48.6% overall, corresponding to 127.9 million people in 2020. This prevalence also increases with age in both men and women. According to the American Heart Association (AHA) 2023 Statistics Update, cardiovascular disease was responsible for an estimated 19.05 million deaths worldwide in 2020 [2,3]. The correlation between obesity and cardiovascular disease (CVD) is a growing and widely recognized epidemic in industrialized countries. Recently, the American Heart Association (AHA) jointly defined this complex network of interrelated health conditions as cardiovascular-metabolic (CMS) syndrome. The molecular mechanisms underlying CMS disease involve a spectrum of interrelated factors, including hyperlipidemia, oxidative stress, lipotoxicity, endoplasmic reticulum stress, and persistent chronic inflammation. Addressing their prevention, management, and treatment is paramount to improving patient health outcomes. Epidemiological data from observational studies and clinical trials provide substantial evidence of significant overlap between metabolic and cardiovascular diseases. Recognizing this complex relationship, the American Heart Association (AHA) recently introduced the concept of a combined disease known as cardiovascular and metabolic syndrome (CMS), emphasizing the close connection and interaction between these health domains [4]. The AHA's recent presidential advisory note discussed the various stages of CMS, with a particular emphasis on the key role of screening and addressing social determinants of health and its impact on the overall well-being of individuals dealing with CMS [5,6,7]. Several other mechanisms are closely associated with CMS, which serve as the basis for the therapeutic management of this emerging condition. This study provides an in-depth analysis of the potential mechanisms involved in CMS and explores the therapeutic approaches available for the effective treatment of this complex syndrome. Furthermore, we highlight the importance of interdisciplinary

collaboration to actively prevent CKM syndrome and improve the holistic health and well-being of individuals with this disease. Notably, CVD remains a common cause of mortality, accounting for 43.6% of all deaths [8]. There are several risk factors that play a significant role in CVD-related morbidity and mortality, and these factors are collectively known as cardiometabolic risk factors [9,10]. Cardiometabolic risk refers to the pathophysiology of CKM syndrome is characterized by a complex interplay of hemodynamic and neurohormonal mechanisms, including sympathetic hyperactivity, various chemical mediators (nitric oxide, prostaglandins, endothelins, etc.), and oxidative stress [11]. According to the presidential advisory note released by the AHA in early October 2023, CKM disease is divided into four distinct stages: stage 0 to stage 4 [12]. Obesity is a key driver of the CKD epidemic and cardiometabolic risk. In the Framingham Heart Study cohort, a weight gain of 2.25 kg or more over 16 years was associated with a 21–45% increased risk of developing the metabolic syndrome. Oxidized LDL is thought to play an important role in the pathogenesis of atherosclerosis. Observational studies have associated α-tocopherol (vitamin E), β-carotene, or both with a reduction in cardiovascular events, but no clinical trials have found any. We conducted a meta-analysis to evaluate the effect of these compounds on long-term cardiovascular mortality and morbidity. The oxidative modification hypothesis of atherosclerosis has prompted the study of antioxidant vitamins in the prevention of the onset and progression of cardiovascular disease. Preclinical studies have shown that supplementation of the diet with various compounds with antioxidant properties before the development of vascular disease suppresses the atherogenic process [13]. These findings have led to several large prospective cohort studies in humans. Therefore, a key element of any preventive program aimed at reducing CKM syndrome is the implementation of comprehensive therapeutic strategies.

**Materials and Methods:**

Experiments were conducted on 240 Wistar albino rats weighing 160-200 g. Fatty liver disease is modeled by a high-fat diet. The animals were divided into four groups: Group 1—intact (healthy); Group 2—rats fed a high-fat diet and in which a model of fatty liver developed over 14, 18, and 20 weeks; Group 3—rats treated with the traditional hepatoprotector Carsil for fatty liver; and Group 4—rats

treated with a new hepatoprotector derived from gossypol for fatty liver for 30 days. Blood biochemistry was performed to determine indicators of hepatocellular insufficiency syndrome.

**Results:** When studying the 14-day results of triglyceride levels in intact rats, its level was 0.4 ± 0.01 mmol / L, and in hepatosis, it increased to 0.93 ± 0.07 mmol / L, but there was no statistically significant difference between them. The amount of TG in the gossypol derivative decreased by 0.75 ± 0.02 mmol / L compared to the intact and control, while in the Karsil preparation its amount was 0.87 ± 0.01 mmol / L, indicating a result close to hepatosis. The indicators reached statistical differences only in comparison with the intact group, while no differences were observed with respect to hepatosis. On the 28th day of the experiment, TG was 0.42±0.01 mmol/L in intact animals and 2.48±0.03 mmol/L in hepatosis, the differences between them were statistically significant ($r1<0.005$). In the gossypol derivative and the drugs, TG was 0.5±0.03 and 0.7±0.01, respectively, and decreased with statistically significant differences from the control ($r<0.005$), but decreased compared to rats in the intact group, reaching statistically significant differences (for both $r1<0.005$). When measuring the level of high-density lipoproteins (HDL) in the blood serum of rats after 14 days, the level was 1.3±0.05 mmol/l in intact animals, and 0.93±0.10 mmol/l in hepatosis, and the difference between them was statistically significant ($r<0.05$). For the gossypol derivative, this indicator was 1.085±0.05 mmol/l, which is significantly higher than the control ($r<0.05$) and demonstrates results close to the indicators of intact animals. The drug Karsil was 0.97±0.16 mmol/l, which is higher than the indicators of the control and intact groups of animals, and a statistically significant difference was observed only in comparison with the intact group of animals ($r<0.01$). When examined after 28 days, the HDL level in hepatosis was 0.75 ± 0.04 mmol / L, which was statistically significantly lower ($r < 0.005$) compared to intact animals (1.3 ± 0.05). In rats administered a gossypol derivative, the serum lipid profile was similar to that in intact animals, 1.25 ± 0.05 mmol / L, and was statistically significantly higher than in the control ($r < 0.005$). In the drug Karsil, although an increase of 1.08 ± 0.16 relative to the control was observed, no statistically significant difference was observed, only a decrease compared to the intact group, with a reliable difference ($r < 0.05$) (Table 1). When studying the level of low-density lipoproteins (LDL) in the blood serum of

experimental rats after 28 days, it was 1.07±0.05 mmol/L higher in intact animals and 2.14±0.04 mmol/L higher in patients with hepatosis, when comparing which a statistically significant difference was observed. In the gossypol derivative, its content was 1.75±0.14 mmol/L and increased compared to intact animals with statistically significant differences (r<0.05); and decreased in hepatosis (r<0.01). A similar result was observed for the comparison drug Carsil (1.94±0.07 mmol/L) (r<0.05; r<0.005, respectively). When examined after 28 days, the LDL level was 4.3±0.05 mmol/L in hepatosis, which was statistically significantly higher (r<0.005) compared to intact animals (1.07±0.05). In rats administered a gossypol derivative, LDL showed results similar to those in intact animals, 1.05±0.05 mmol/L. In the Karsil preparation, although an increase of 1.78±0.16 relative to the control was observed, no statistics were observed, but only a decrease compared to the intact group, with a reliable difference (r<0.05) (Table 2).

**Table 1 The effect of gossypol derivative on biochemical parameters of liver function in rats with fatty hepatosis model, (M±m; n=10)**

| Groups<br>Indicators | intact | hepatosis |
|---|---|---|
| **Before treatment** | | |
| **Triglyceride, mmol/L** | 0,0578±0,001 | 0,084±0,001 |
| **HDL, mmol/L** | 0,0255±0,001 | 0,011±0,001 |
| **LDL, mmol/L** | 0,038±0,002 | 0,071±0,002 |

**Table 2 The effect of gossypol derivative on biochemical parameters of liver function in rats with fatty hepatosis model, (M±m; n=10)**

| Groups<br>Indicators | intact | hepatosis | Groups<br>Indicators | intact |
|---|---|---|---|---|
| **After 14-week treatment** | | | | |
| **Triglyceride, mmol/L** | 0,058±0,001 | 0,09±0,003 | 0,073±0,02$^{\#}$ | 0,09±0,01$^{\#\#\#}$ |
| **HDL, mmol/L** | 0,025±0,001 | 0,009±0,001 | 0,02±0,05* | 0,01±0,16$^{\#\#}$ |
| **LDL, mmol/L** | 0,037±0,002 | 0,187±0,002 | 0,136±0,19*,$^{\#\#}$ | 0,178±0,02*,$^{\#\#\#}$ |
| **Atherogenicity coefficient %** | 1,48 | 20 | 6,8 | 17,8 |
| **After 28-week treatment** | | | | |
| **Triglyceride, mmol/L** | 0,059±0,001 | 0,114±0,02$^{\#\#\#}$ | 0,06±0,01***,$^{\#\#\#}$ | 0,178±0,08***,$^{\#\#\#}$ |
| **HDL, mmol/L** | 0,0255±0,011 | 0,0126±0,03$^{\#\#\#}$ | 0,0252±0,01*** | 0,016±0,003$^{\#}$ |
| **LDL, mmol/L** | 0,037±0,13 | 0,267±0,1 | 0,04±0,03*,$^{\#\#\#}$ | 0,0506±0,06*, |
| **Atherogenicity coefficient %** | 1,48 | 21,2 | 1,6 | 3,16 |

*Note. *r<0.05, **r<0.01, ***r<0.005 statistically significant differences compared to the control group; #r<0.05, ##r<0.01; ###r<0.005 statistically significant differences compared to the intact group.*

## Conclusion

Thus, when analyzing the experimental results for TG indicators by day 28, the test drugs, the gossypol derivative and Carsil, decreased relative to the control with a statistically significant difference. In terms of HDL indicators, the gossypol derivative achieved statistically significant differences from the control on days 14 and 28 of the experiment, showing results close to those in intact animals. Although LDL indicators were higher in the study samples compared to the group of intact animals, they reduced its quantitative indicators, showing statistically significant differences from the control. Triglyceride and LDL levels were higher in the group with hepatosis. The results suggest that the gossypol derivative and the reference drug, Carsil, exert a positive effect on serum lipid parameters in rats with fatty liver disease, with the efficacy of the gossypol derivative and Carsil being higher than that of Carsil. Cardiovascular and metabolic diseases interact at the pathophysiological level, leading to a clinical overlap manifested in the broader cardiometabolic syndrome (CMS). These three areas of health share common underlying mechanisms, the activation of which initiates a detrimental cycle, perpetuating disease processes and increasing morbidity and mortality. The complex interplay of cardiovascular and metabolic diseases highlights the need for further research. The intersection of various aspects of cardiovascular disease, obesity, and metabolic syndrome (CMS) highlights the importance of a holistic approach to understanding and treating these interrelated health conditions. Since the use of the new hepatoprotector, a derivative of gossypol, significantly reduced the atherogenic index, thereby reducing the risk of vascular atherosclerosis, which is a pathogenetic mechanism for the development of cardiometabolic syndrome and the risk of cardiovascular complications.

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