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Circulating Levels of Human Fibroblast Growth Factor 21 are Associated with LDL in Patients with Coronary Artery Disease

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Abstract: **Background:** An enzyme called "HFGF21" promotes the hepatocytes' degradation of the low-density lipoprotein receptor (LDL-R). HFGF21 inhibition has emerged as a new target for lipid-lowering medication. Three different types of monocytes are essential to the pathophysiology of atherosclerosis. The purpose of this study was to ascertain if circulating levels of HFGF21 and LDL-liped subgroups are related.

Supplies and Methods: We gathered seventy people with coronary artery disease for our study. Levels of HFGF21, LDL liped, and 30 control health were measured.

Results: Eighty percent of the cases involved men, whose ages varied from 40 to 70. Compared to 30 male controls, patients had greater levels of HFGF21. In patients, CM was associated with circulating levels of HFGF21, but NCM was inversely correlated with these levels. Individuals whose levels of HFGF21 above the median had a noticeably higher

Conclusions: Changes in lifestyle are substantially associated with elevated serum FGF21 levels. smoking, eating a diet high in calories from fat and carbohydrates, taking amino acids, The study shows that risk factors like smoking, high blood pressure, diabetes, obesity, and physical inactivity are strongly correlated with the diagnostic catheterization procedure.

Keywords: Human Fibroblast Growth Factor 21, coronary artery disease, low-density lipoprotein (LDL).

INTRODUCTION:

The most common causes of stroke in the Western world are heart disease and stroke, especially coronary artery disease (CAD). It is dependent on cholesterol, which is the primary cause of CAD, a blood pressure-related inflammatory illness. [1] that involves secreted low-density lipoprotein (LDL). Deep layer penetration from the blood pressure wall where it is required and submitted to a desired adjustment. This incident is caused by a powerful inflammatory outbreak that causes a single stroke and transfers to the internal layer[2]. A study of continuous inflammatory surgery that focuses on cytokines and bladder surgery, for example, obvious ulcers, or on the shape of the chest wall Coronary Artery Synthesis (ACS). Numerous studies have demonstrated a causal link between LDL cholesterol and boards' ability to draw in clients. These investigations include genetic and genetic research as well as epidemiological and interventional studies.[3]. Therefore, LDL-cholesterol-lowering cornerstones are preferred in secondary cardiovascular interventions. Examples of statins and azithromycin angle stones in lowering LDL-C therapeutic, with the presence of the latest active adrenaline inhibiting agent such as human fibroblasts 21 suitable for

patients with pneumonia Offers for the sake of the higher. The enzyme PCSK9, which was initially identified in a family with familial hypercholesterolemia, is in charge of the subsequent transition of LDL into the liver cells. Future LDL can be further re-regulated by antigens like human fibroblasts 21.[4]. Thus, iodine is used to increase the regulation of LDL cholesterol levels associated with liver gaps, but iodine is used to inhibit the ratio of low-density blood cycle's LDL cholesterol. There is little proof of the potential role. of PCSK9 in inflammatory diseases. Inflammatory surgery is widespread in all stages of CAD, from the beginning and progress to the stability of the blackheads[5]. CM is described as exhibiting classical blank behavior, whereas IM is described as a strong inflammatory behavior because NCM exhibits a distinctive distance behavior specific to blood wall. Several references were obtained from the receiving studies to the distinctive walls of the individual subgroups at all stages of the solar system[6]. Because This study aims to assess the association between LDL cholesterol and blood cycle pain, since the immune system and LDL cholesterol interact to influence the beginning of stroke. Consider the development of natural immunity and the levels of human fiber 21.[7]

Materials & methods

Ninety adults who appear to be in good health make up the subject group. For males, their ages varied between 30 and 79. In the holy city of Karbala, samples were gathered at the Imam Hussein Medical City's Karbala Center for Heart Diseases. Among the 90 male samples that were included in the study, 60 had coronary artery catheterizations performed at the same institution and had heart ischemia and cardiovascular disorders. In addition, 30 people participated in the study between November 2022 and December 30, 2023, during which time the patient, the center's physician filled out the form with accurate information about the patient's age, weight, blood pressure, and any inherited conditions. After obtaining official consent from the patient and the center's administration to perform the required tests, blood was extracted.

Collecting blood samples

blood taken from an antecubital vein in the morning before coronary angiography. After discarding the first 3 ml of blood, the blood was drawn into an ethylenediaminetetraacetic acid (EDTA) tube (Bio-One, Greiner). Before being taken to the Vienna General Hospital's central laboratory for standard laboratory parameters, the residual For further analysis, the blood was stored at 80°C after being centrifuged at 3 thaw sent rpm and 4°C.

Human Fibroblast Growth Factor 21 measurement

Following the manufacturer's procedures, the blood levels of HFGF21 were measured using a particular ELISA with an assay range of 0.6 to 40 ng/mL.

Measurements in the laboratory

Interleukin-6 levels were measured using ELISAs and IL-4, IL-10, monocytes (MCP-1) and tumor necrosis factor alpha (TNF-α) levels were measured in blood plasma. [8]

Lipid measurements

Using enzymatic methods, which included triglycerides, LDL, HDL and VLDL. [9] .

Statistical analysis

The counts and percentages representing categorical variables were compared using the 2 or Fisher's exact test, as appropriate. The median and interquartile range (IQR) are used for continuous variables. The Spearman's correlation coefficient was calculated after the data were compared using the Mann-Whitney test. The existence of diabetes, hypertension, BMI, and smoking status are traditional cardiovascular risk factors using SPSS 2025 [10].

Experimental design

Ninety patients with angina pectoris, a clinical sign of coronary artery disease, were split into two groups for this case-control research (60). This group was then subdivided into three four groups

based on related problems {snookering man n = 36, non-snookering man n = 24, Man with hypertension 40, and the mean pressure about 20}, and age-based groups {(40-49) n = 15, (50-59) n = 20, (60-69) n = 25}. Based on related circumstances, this subgroup is divided into three groups: unstable angina (n = 15), stable angina (n = 15), and myocardial infarction (n = 30). Figure (3-1) and the percentage of fat in patients relative to control were also computed, and body mass was classified as normal (n = 20), obese (n = 20), and a significant increase in weight (n = 20). Characteristic chest pain, positive ECG and angiography alterations, and an estimate of positive cardiac indices were used to diagnosis the patients. Thirty guys from the heart's coronary care unit (CCU) at Imam Hussein Medical City/Karbala Center for Diseases who had no prior history of infection were recruited as a control group for the trial between January and August 2023. Control men are selected from family members and an outpatient clinic if they have no history of ICU hospitalization, chest pain, and a normal resting ECG.

Ethical approval : Since no patients were involved and all human rights were upheld, the study was carried out on animals. Document number 6289 states that the research protocol was evaluated and approved by a local on June 12, 2022.

The main problem: Infarkii Galan irratti dhukkubsattoota kateeterii onnee booda hospitaala dafanii adda baasuu fi tilmaamu

Results

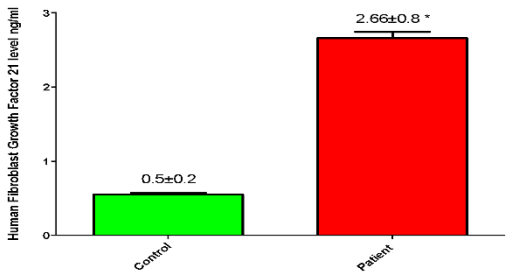


Figure 1 The HFDG21 levels in patients and controls are contrasted in Figure 1. Compared to controls, HFDG21 levels in patients were considerably higher (P<0.05). Controls number thirty. Patients = 60 signify significance (P<0.05).*

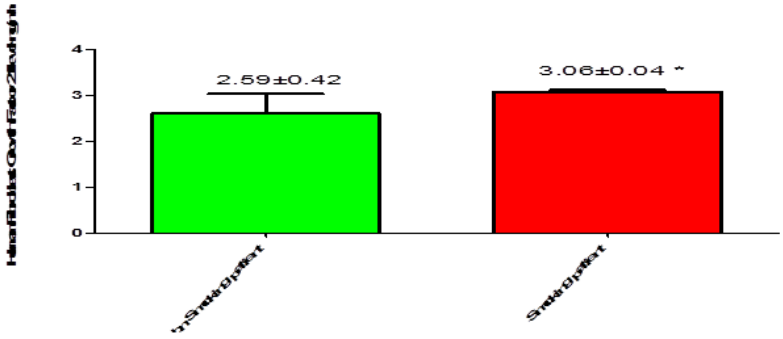
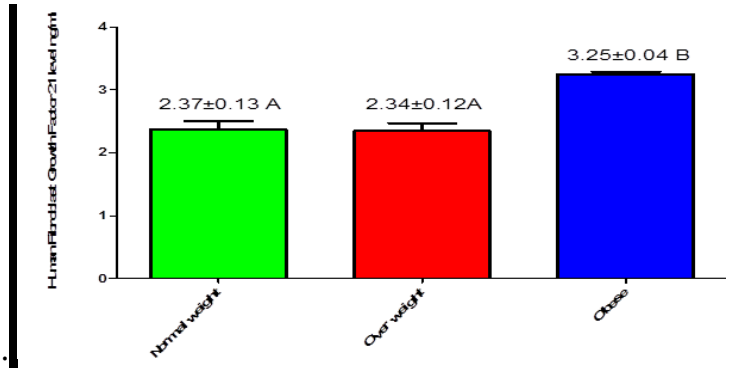
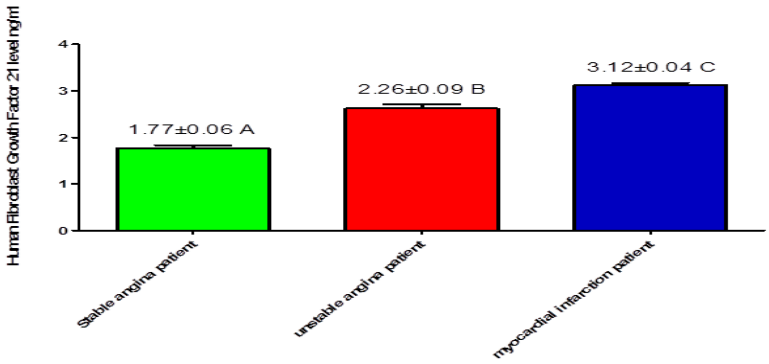


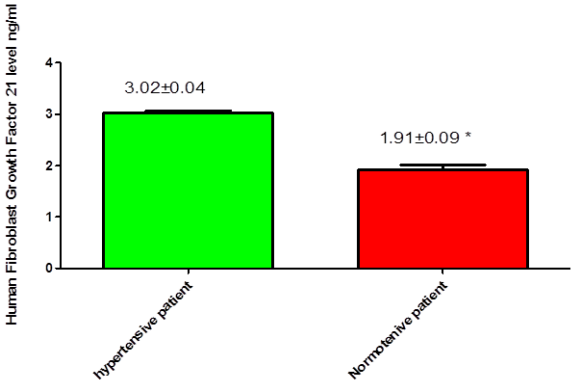
Figure (2). The levels of HFGF21 in patients who smoke and those who do not are compared. Compared to smoking patients, non-smoking patients had considerably lower levels of 21 (P<0.05) (2.). The quantity of samples indicates that the data is significant (P<0.05): There are 36 smokers and 24 non-smokers.



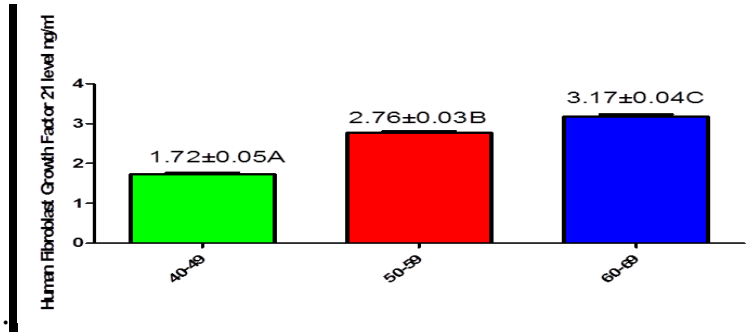
*HFGF21 levels in normal weight patients are compared to those in overweight and obese patients in Figure (3). When compared to obese patients, the levels of HFGF21 were significantly lower (P<0.05) in normal and weight andnon overweight patients (3). t. Sample count: Normal weight = 20, Overweight = 20, Obese aboiut 20, * Significant (P<0.05) is inedicated by different letters.*



*HFGF21 levels in patients with stable angina are compared to those with unstable angina and myocardial infarction patients in Figure (4). HFGF21 levels were significantly lower (P<0.05) in patients with stable angina than in those with unstable angina and myocardial infarction (figure 4-38). There were 15 patients with stable angina, 15 with unstable angina, and 30 with myocardial infarction. * Different letters indicate significant (P<0.05).*



*HFGF21 levels in hypertensive and normotensive patients are contrasted in Figure (5). HFGF21 levels in hypertension patients were significantly lower (P<0.05) than in normotensive patients (4). The quantity of samples Significant (P<0.05) is indicated by stable angina patient = 40 and unstable angina patient = 20**



*HFGF21 levels by age are displayed in Figure (6). When compared to obese patients, the levels of HFGF21 were significantly lower (P<0.05) in normal weight and overweight patients (6). * Various letters indicate significant (P<0.05). Number of samples: 40-49 years n = 15, 50-59 years n = 20, 60-69 years n = 25.*

Discussion

A link was found between PCSK9 levels in those with coronary artery disease in the results of the current study, where 69 patients with stable coronary artery disease Compared to smokers, nonsmokers had a considerably reduced level of HFGF21 (P 0.05) (figure 4-5). The levels of HFGF21 in smokers and nonsmokers are shown in Figure (4-5). Smokers = 36* and nonsmokers = 24* indicate a significant number of samples (P0.05).Recent research indicates that smoking is the leading cause of illnesses and avoidable deaths in contemporary society. Smoking is known to be a significant risk factor for a number of illnesses, such as metabolic and cardiovascular conditions. Numerous studies have shown that FGF21 has anti-inflammatory qualities. By boosting the synthesis of proinflammatory cytokines like interleukin, smoking is known to induce inflammation. [8].

This meta-analysis and other recent studies have shown that smoking dramatically increases cFGF21 levels, indicating that this is a compensatory response to smoking-induced inflammatory stress. Lifestyle modifications are significantly linked to increased serum FGF21 levels. A high-carbohydrate diet, a high-calorie, high-fat diet, smoking, and excessive calorie intake can all increase it. Increased hepatic fatty acid oxidation, decreased hepatic triglyceride accumulation, improved insulin sensitivity, and preference suppression are only a few of the metabolic regulating activities of the amino acid FGF21. Smokers use the central nervous system to absorb sugar. [11]

Long-acting FGF21 analogues successfully reduced blood lipids, increased serum adiponectin levels, and had a variety of weight-loss benefits in people, although without lowering plasma glucose levels. [12] .

According to the current study, elevated cFGF21 is a useful biomarker for evaluating the effects of metabolic responses and may aid in the management of metabolism. A recent meta-analysis and thorough review of the literature shown that different lifestyles significantly impact cFGF21 levels. A preventive and/or compensatory response to inflammation and stress in stressful settings, as well as alterations in the cardiovascular and metabolic systems brought on by lifestyle changes, may be predicted by elevated cFGF21 levels. [3] When compared to obese patients, the level of HFGF21 was significantly lower (P<0.05) in normal weight patients, overweight patients, and obese patients. Sample count: Normal weight = 20, Overweight = 20, Obese = 20, * Significant (P<0.05) is indicated by different letters.

Elevated levels of cFGF21 are linked to obesity, and the predicted benefits of FGF21, such as improved glucose tolerance and decreased plasma glucose and fat levels, are reduced or even abolished in obese individuals, suggesting a FGF21-resistant state. Numerous parameters, including the quantity and kind of participants, have an impact on CRIWL-induced cFGF21, and CRIWL at the cFGF21 level has been inconsistent. the amount of weight reduction, the duration of the dietary intervention after the intervention type and end measure [13]. Using 30% of calories from protein as a cut-off value with the change, we found that the diet's protein content can have a significant role.

While doubtful findings were produced with very low dietary protein amounts (30E% protein) or with a diet with an unclear protein content, the bulk of CRIWL decreasing cFGF21 outcomes were obtained with relatively high dietary protein contents (30E% protein). According to a recent sophisticated assessment, CR without malnutrition may reduce the burden of disease and lengthen both human and animal lifespans. [5]

Even with higher total calorie intake, it simultaneously restored the protein shortfall caused by VLCD and blocked the cFGF21 upregulation caused by protein deficiency, resulting in a general reduction in cFGF21 levels. [14]

FGF-21 levels were significantly correlated in both analyses of our study, suggesting a meaningful relationship. Indeed, it has been reported that FGF-21 secretion is physiologically stimulated in both humans and animals..[2] Recent studies have also demonstrated that FGF-21 improves the underlying pathologic processes of MetS and NAFLD by reducing insulin resistance, increasing DMT2 which is typically linked to MetS and NAFLD, upregulates FGF-21. FGF-21 was also not associated with HOMA insulin resistance, obesity, or NAFLD features. [15]

After a period of non-malnutrition, declining cFGF21 levels may indicate decreased body fat because several research have shown that obesity and liver fat content are linked to increased levels of cFGF21. Conversely, protein restriction affects the amount of cFGF21. Therefore, there are two ways that protein deficit can change cFGF21 levels: upregulation through protein deficiency and downregulation through CR-induced fat loss. The different observations may be explained by this. [16]

HFGF21 levels in patients with stable angina were significantly lower ($P<0.05$) than those with unstable angina and myocardial infarction. There were 15 patients with stable angina, 15 with unstable angina, and 30 with myocardial infarction. * Different letters indicate significant ($P<0.05$). Recent studies indicate that FGF21 is an endocrine FGF21 and that locally produced FGF21 appears to be centralized in the heart. Following heart injury, adipose tissue produces FGF21, which functions through myocardial infarction signaling, FGFR1, or stable or unstable angina patients. X Liu ,This supports the finding of a previous study that FGF21 levels can predict morbidity and death in individuals with coronary heart disease, myocardial infarction, and stable or unstable angina. [17]

FGF21 was produced and released by cardio myocytes, according to a prior study. In order to avoid isoproterenol-induced cardiac hypertrophy, In individuals with myocardial infarction, unstable angina, and stable angina, cardiac FGF21 was produced in response to cardiac ischemia stress.[15].

This result is in contrast to that of Sunaga et al., who discovered that blood FGF21 levels were noticeably higher in patients with AMI following PCI. Additional research showed a connection between FGF21 and AMI. Consistent with our findings, Chen et al. found that FGF21 was associated with myocardial infarction in coronary heart disease and AMI. [16]

MI and I/R damage result in apoptosis and myocardial infarction, which impair heart function. By activating the PI3K-Akt1-BAD pathway and Akt-GSK3b-caspase apoptosis, exogenous FGF21 shields cardiac myocytes against apoptosis and myocardial infarction and enhances cardiac function in FGF21-KO mice. It has been shown that by turning on these pathways, myocardial infarct area may reduce and heart function may rise. A summary of the data supporting FGF21's role in preventing cardiovascular cell death in in vitro models is provided. By boosting energy supply and reducing inflammation and apoptosis, FGF21 dose-dependently shields H9c2 cells from I/R damage. Akt-GSK3b pathway-mediated caspase 3-dependent pathways in H9c2 cell lines [18]

Previous studies found that FGF21 was synthesized and released upon activation of the peroxisome proliferator-activated receptor alpha (PPARa). By autocrinely reducing DNA fragmentation, FGF21, when added to culture medium, shielded CMECs against Ox-LDL-induced lipotoxicity. Recombinant rat FGF21 injection 10 minutes prior to ischemia was shown to protect the heart against I/R damage in an ex vivo model of global myocardial ischemia by reducing MI and improving cardiac function through activation of the MAPK-PI3k-Akt signaling pathway. [19] .

Additionally, the study discovered that the Sirt1-PPARa pathway plays a crucial role in controlling the production of FGF21 in the heart. According to in vivo data, FGF21-KO animals that received a constant intravenous infusion for days developed cardiomyopathy, which led to MI, a reduction in cardiac metabolism, and a loss of cardiac function in the rat heart. [20]

The skeletal muscle-produced FGF21 endocrine function reduced cardiac hypertrophy and reversed the unfavorable cardiac remodeling process in this chronic MI animal model, improving left ventricular function. Planavila et al. (2013) claim that FGF21 decreases hypertrophic markers like skeletal actin (aSKA) and atrial natriuretic factor (ANF) in order to lessen cardiac hypertrophy. It has been demonstrated that FGF21 improves cardiac function and decreases the cardio myocyte area and heart weight/body weight ratio. Planavila and associates (2014) To sum up, it has been demonstrated that FGF21 guards against heart hypertrophic injury. On the other side, it was shown that FGF21 deficiency increases the development of ventricular hypertrophy via influencing cardiac metabolism, oxidative stress, proinflammatory pathways, and cardiac fibrosis. [21]

Combined, these results indicate that both endogenous and exogenous FGF21 contribute to the protection of the heart against apoptosis through a variety of pathways, including Akt-GSK3b-caspase 3 and PI3K-Akt1-BAD, which reduce infarction and increase left ventricular function in the context of I/R injury, lipotoxic infarct area, and MI conditions. Additionally, FGF21 increased energy supply while shielding cardio myocyte lines from oxidative damage. The most common cause of myocardial infarction is coronary artery disease (CAD), which causes ischemia of the heart. This condition can affect cardiac function by lowering the ejection fraction, which prevents enough oxygen from reaching bodily tissues and can lead to the development of cardiac hypertrophy and heart failure because of the heart's compensatory mechanisms. Maintaining EF and delivering oxygen to peripheral metabolic areas need cardiovascular remodeling. Long-term effects of this maladaptive remodeling process may include increased ventricular dilatation, ventricular hypertrophy, interstitial growth, and heart fibrosis. [22].

When comparing hypertension patients to normotensive patients, the level of HFGF21 in the former exhibited a substantial decrease ($P<0.05$). Sample count: 40 patients with stable angina, 20 patients with unstable angina Significant ($P<0.05$) is indicated with a *. Plasma FGF21 Serum FGF21 levels were shown to be strongly correlated with carotid artery intima-media thickness, lower extremity atherosclerotic disease, waist size, and systolic blood pressure in individuals with type 2 diabetes. FGF21 was also proven to be an independent risk factor for atrial fibrillation (AF) and to be elevated in AF patients. In patients of NAFLD and CAD, serum FGF21 was linked to a negative steatotic profile and a positive connection with triglycerides (TG) and total cholesterol (TC). Additionally, it was discovered that the serum levels of FGF21 in CAD patients were negatively linked with HDL and ApoA1 but favorably correlated with TG, fasting blood glucose, ApoB100, insulin, and HOMA-IR. [23]

Recent studies have connected blood levels of FGF21 to a patient's metabolic state. Systolic blood pressure is associated with higher serum FGF21 levels. Ex vivo investigations using obese rat hearts and in vivo tests using DIO rat livers and white adipose tissue have shown that FGF21 resistance is responsible for a number of degenerative diseases of the heart that are brought on by metabolic dysregulation. The prognosis of cardiovascular disease and detrimental metabolic dysregulation may be indicated by serum FGF21 levels. Initially, Patel and associates proposed the term "FGF21 resistance" in the heart of chronic DIO mice. They found that the protein FGF21 mRNA, FGF21, was expressed and secreted at higher quantities in the hearts of fat mice. This condition has been linked to decreased ERK1/2, Akt, and AMPK as well as disruption of FGF21-FGFR1-b-Klotho signaling, despite the elevated amount of FGF21. [10]

These results suggest that the FGF21 signaling cascade was hindered by obesity, and that a feedback mechanism allowed for increased FGF21 production to make up for the lack of FGF21 receptor signaling. Regretfully, the elevated endogenous FGF21 level was insufficient when exogenous FGF21 was introduced. It supports the treatment strategy. Clinical investigations have

also documented FGF21 resistance, with metabolic syndrome of non-NAFLD coronary heart disease showing significantly elevated serum FGF21 levels. [24]

FGF-21 helps to reduce insulin resistance, boost insulin-independent glucose absorption in 3T3-L1 adipocytes, regulate WAT lipolysis, and ultimately alleviate the underlying pathogenic processes of NAFLD and MetS. Unexpectedly, FGF-21 was linked to an increase in blood pressure. Obesity-induced MetS and NAFLD are generally associated with MetS and NAFLD. Furthermore, FGF-21 was not associated with any traits of insulin resistance associated with MetS, NAFLD, or HOMA. [23].

When compared to obese patients, the level of HFGF21 was significantly lower ($P<0.05$) in normal weight and overweight patients. HFGF21 levels vary with age. The quantity of samples: * Different letters indicate significant ($P<0.05$). 40-49 years n = 15, 50-59 years n = 20, 60-69 years n = 25.

Recent studies have shown that many of the hormones and chemicals involved in development, maturation, and the maintenance of systemic physiological needs change with age, in addition to changes in body composition. In a number of age-related pathophysiological processes involving oxidative stress and energy metabolism, PPARs are essential regulators. PPARa and PPARg have been demonstrated in several studies to reduce the production of inflammatory genes, including cytokines, metalloproteinases, and acute phase proteins, and they are also linked to bone resorption (catabolic) processes. Future research should examine how certain hormones and transcription factors affect the production and release of FGF21. Younger people's FGF21 levels may be more influenced by age, which might be explained by variations in underlying regulatory factors and pathways that are also impacted by aging. Disparities [25]

Think about a few key advantages. In summary, we found that circulating FGF21 increased with age in healthy individuals, suggesting a possible differential age impact in response to metabolic load throughout the course of life. At low levels of FGF21, however, the age-related association may be explained by bone density. Given our findings presented here and the importance of FGF21 in cellular energy metabolism as a regulator of fat and glucose consumption in animal models, the question now is whether age-related increases in FGF21 are causative or a consequence of body composition. Skeletal muscle is the main location of glucose absorption under normal conditions, and it is known that muscular contraction has insulin-like effects on glucose uptake in skeletal muscle protein isolate. [26].

TG, VLDL, LDL, and HDL values did not differ statistically significantly across the groups in this study. These modifications in training groups, however, differed considerably from the control group. While other studies produced contradictory outcomes, these findings are in line with previous research. Numerous cardiovascular diseases seem to be caused by juvenile obesity and related abnormalities. [6]

According to the aforementioned study findings, the training group's blood LDL and TG levels dramatically dropped following three months of endurance training, however serum HDL levels did not significantly rise [5]. Researchers hypothesized that this may occur as a result of the aforementioned study's inadequate home exercise intensity. However, following treatments, HDL dramatically rose in training groups in the current study. [23]

Regular exercise can lower blood lipid levels, including LDL, TG, and TC, and boost VLDL and HDL, which can prevent the development of atherosclerotic plaques, according to another study. Because it is linked to the secretion of blood lipid profiles and cardiovascular risk factors, several studies have demonstrated that practice can reduce body fat mass. In another study, Kim and his colleagues looked at how 12 weeks of consistent endurance exercise affected serum adiponectin, insulin resistance, and blood lipid profile levels in teenage students with a body mass index over[27]

According to another study, FGF21 plays a significant part in energy balance and the metabolism of fats and carbohydrates. By interacting with beta-3 adrenergic receptors on epinephrine in adipose tissue, FGF21 can promote lipolysis. Through the effect of insulin, it can also lower blood glucose

levels. Muscle glucose absorption and the transfer of GLUT4 to the cell membrane are the results of this function, which is carried out via the AMPK signaling pathway. Nevertheless, little is known about how it functions in human physiological settings. It has been demonstrated that FGF21 enhances lipolysis and metabolic alterations by raising catecholamines and lowering serum insulin. As previously mentioned, FGF21 can impact insulin (insulin resistance), glucose, lipid metabolism, and lipid profiles.

Conclusion

Cardiovascular risk factors linked to obesity are improved by endurance exercise, resistance training, and combination training. These training techniques also help school-aged obese children's cardiovascular risk factors. For some individuals, they can also serve as efficient workout regimens. In order to reduce the prevalence of cardiovascular risk factors and obesity-related illnesses in obese boys, EET, RET, and CET—especially EET—can be suggested as a non-medical approach.

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