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Current pharmacological approaches in obesity treatment

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ABSTRACT

Obesity is a complex disorder and affected by so many factors in which the balance between food consumption and calorie usage is disrupted. Drugs that act on appetite, food intake, calorie absorption or calorie consumption, or a combination of these, are basically central or peripheral agents. Diethylpropion and phentermine are preferred for short-term obesity treatment. Orlistat, lorcaserin, topiramate/phentermine, naltrexone/bupropion, and liraglutide are preferred for long-term obesity treatment. The main drugs whose experimental and clinical phase studies are still ongoing are setmelanotide, zonisamide/bupropion, neuropeptide Y antagonists, semaglutide and oral glucagon-like peptide-1 agonists, cannabinoid type-1 receptor inhibitors, amylin mimetics, amylin/calcitonin receptor activators, glucose-linked insulin-like acting peptide analogues, dual-acting glucagon-like peptide-1/glucagon receptor agonists, peptide YY, leptin analogues, beloranib, cetilistat, tenofensin, fibroblast growth factor-21 and obesity vaccines. While managing the treatment of an obese patient, considering the large costs of the disease and the high incidence of disorder, pharmacotherapeutic agents are not enough to meet the clinic spectrum like adverse effects and contraindications, but new drugs and studies in this field offer hope to the medical world in terms of efficacy and safety profile. However, it would not be rational to expect miracles from drugs without a change in lifestyle in the magement of this disorder.

Keywords: Obesity, new drugs, pharmacology, weight loss medications, weight management

Obesity is a multifactorial disorder that is described as high amount fat storage that can impair human health, alters anatomy and physiology, and therefore occurs with metabolic, biomechanical and psychosocial problems. The disease, in which the ratio between food consumption and calorie usage is disrupted, is affected by many physical and environmental situations. Although the Body Mass Index (BMI, kg/m²) does not distinguish between the proportion between fat and lean body mass, it is the most useful parameter. [1]

MEDICATIONS USED IN THE PAST FOR TREATMENT OF OBESITY

As a consequence of the observation of the relationship between hypothyroidism and obesity, the first drug used was thyroid hormone. Provided weight loss, but 80% of the weight lost is muscle tissue. After the treatment was terminated, weight gain was observed again due to thyroid gland atrophy. Obesity has been avoided due to the risk of tachycardia, cardiac arrhythmias and sudden death in excessive use.

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Dinitrophenol was introduced in 1933 for the treatment of obesity. It disrupts oxidation reactions and increases metabolic rate. It has been used together with thyroid hormone and has been effective. However, its use was discontinued due to its serious toxic effects (hepatotoxicity, agranulocytosis, visual impairment, dermatitis, death).

Amphetamine was preferred in the treatment of obesity in the late 1930s. Although it was used in combination therapy with thyroid hormone, digitals and diuretics between 1940-1960, it resulted in myocardial toxicity, development of addiction to some other substances in the drugs and sudden death.

Aminorex was introduced in the 1960s but was gathered from the drug stores in 1968 because of the pulmonary hypertension.

Fenfluramine is an agent that increases synaptic serotonin release and inhibits its reuptake. In 1997, fenfluramine and dexfenfluramine were withdrawn from drug stores when it was reported that they could cause valvular cardiac problems.

Phenylpropanolamine is a sympathomimetic. It was gathered from the drug stores as it raised the probability of stroke.

Sibutramine was found in the USA in 1997 and has been approved by the Food and Drug Administration (FDA). It suppresses appetite and increases thermogenesis by reuptake blockage of serotonin and norepinephrine. It improves the serum lipid profile and reduces body weight by approximately 4.5 kg in one year. In 2010, it was first removed from the market by the European Medicines Agency (EMA) after increasing the risk of MI (myocardial infarction) in clinical trials. Today, many debilitating drugs can be found illegally in non-pharmaceutical products. 1

DRUGS THAT FDA APPROVED USED IN THE SHORT-TERM TREATMENT FOR OBESITY

Phentermine

In 1959, it was authorized by the FDA for short-term (≤ 12 weeks) weight control purposes. It decreases appetite due to the release of norepinephrine in the central nervous system. The efficacy and safety of 30 mg controlled-release phentermine was evaluated in a 1.5-month clinical trial in diabetic, dyslipidemic, or obese with hypertension. [2] A significant weight loss was observed in patients given phentermine compared to placebo, and their total cholesterol and low-density lipoprotein (LDL) levels improved. There was no difference between the groups in systolic and diastolic blood pressure. In a 36-week placebo-controlled study evaluating 108 obese patients, 30 mg of phentermine daily was given regularly or intermittently. While there was a weight loss of 4.8 kg in the placebo, there was a mean weight loss of 12.2 kg and 13 kg, respectively, in the drug groups. The most common side effects in the study were dry mouth and sleep disturbances, while serious complications were palpitations, increased heart rate, and hypertension. It has been stated that longer-term, dose-adjusted clinical studies are required to confirm phentermine's efficacy and safety in treating obesity. [3]

Diethylpropion

It is a sympathomimetic amine with amphetamine-like effects and suppresses appetite by increasing the secretion of norepinephrine and dopamine and inhibiting their reabsorption. Approved by the FDA for use in less than 12 weeks. It causes about 10% weight loss in a year. It is given orally at a dose of 25 mg three times a day or in the extended pharmaceutical form at a dose of 75 mg once a day. Long-term use can cause pulmonary hypertension and heart valve disease like other appetite suppressants with amphetamine-like effects. If these symptoms occur, the drug should be discontinued, and the patient should be evaluated immediately. It is contraindicated for advanced atherosclerosis, severe hypertension, hyperthyroidism, glaucoma, agitation, history of drug dependence, MAO inhibitors during or within two weeks of use, and concomitant use with other anorectic drugs. Cardiac arrhythmia, cerebrovascular accident, hypertension, anxiety, depression, dizziness, euphoria, headache, hyperarousal, precordial pain, psychosis, alopecia, skin rashes, libido changes, gynecomastia, constipation, diarrhea, dysphagia, nausea, vomiting, Many adverse effects may occur, including xerostomia, bone marrow depression, dyskinesia, myalgia, tremor, blurred vision, and mydriasis. [4] In a meta-analysis of studies lasting 6-52 weeks involving approximately 80% of women receiving concomitant lifestyle treatments, diethylpropion produced a weight loss of 3 kg. [5]

FDA ALLOWED AGENTS USED FOR LONG-PERIOD MANAGEMENT OF OBESITY

Orlistat

It is currently the longest-licensed anti-obesity

agent for long-term management. The FDA approved it in 1999. It is prescribed at 120 mg for people over 12 years old. After oral intake, within 3-5 days, almost all of it is excreted with feces; its systemic absorption is close to zero and does not accumulate. Unlike other agents, it does not affect appetite. Its primary mechanism of action is the inhibition of intestinal absorption of triglycerides. In addition, it prevents the release of gastrointestinal system lipases and provides approximately 30% calorie reduction.

In a study of 3305 patients, a weight loss of 2.4% was achieved at the end of four years and reduced the risk of type 2 DM compared to a placebo. It also reduced fat absorption and improved lipid profiles, blood pressure, and insulin sensitivity. In another study, 91 percent of subjects given orlistat experienced gastrointestinal side effects, and 8 percent of these patients dropped out of the study because of this. [6] Common gastrointestinal adverse effects are gas, bloating, indigestion, abdominal pain, and diarrhea. It is prescribed daily multivitamins because of the risk of fat-soluble vitamin deficiency. In some cases, acute kidney injury has been reported in orlistat users with diabetes-like metabolic problems. [3]

Lorcaserin

It is a selective 5-hydroxytryptamine (5-HT) 2C receptor stimulant. The use of 10 mg twice daily was approved by the FDA in 2012, and on February 14, 2020, patients were asked to warn of potential cancer-related risks. Activating proopiomelanocortin (POMC) receptors in the body reduce calorie consumption and increases satiety with serotonin's anorectic effect. It has a high specificity against the 5-HT2C receptor. Therefore, it suppresses starvation and hunger without leading to pulmonary hypertension and heart valve defects. Existing trials have shown that it has psychological effects that contribute to weight loss, reduce appetite and the urge to eat, and increase satiety.

The efficacy and safety of different doses of lorcaserin have been studied in clinical trials called BLOOM and BLOSSOM. All volunteers received dietary and physical activity counselling. In the BLOOM study, 3182 volunteers with a BMI of 30-45 kg/m^2 were given 10 mg of lorcaserin or a placebo for 52 weeks. The drug-administered group received the same dose of lorcaserin or placebo for another 52 weeks. Weight loss rates of 10% and above were 22.6% in the lorcaserin group and 7.7% in the placebo group. 7 The BLOSSOM study consisted of 4008 individuals with a BMI of 30-45 kg/m^2. Volunteers were given 10 mg of lorcaserin or a placebo 2 or 4 times daily. After 52 weeks, the lorcaserin group was attenuated by more than 10% compared to the placebo. 22.6% of the group taking lorcaserin 10 mg four times a day and 17.4% of the group taking it twice a day lost more than 10% of their weight. This rate was 9.7% in the placebo group. In a clinical study evaluating the risk of lorcaserin abuse, effects were assessed using a visual analog scale by giving participants ketamine, zolpidem, lorcaserin, and a placebo. This study determined that lorcaserin was well tolerated and had no risk of abuse. [8] The main adverse effects of the drug are headache, dizziness, nausea, dry mouth, hypoglycemia, cough, constipation, back pain, and fatigue. Since it activates the serotonergic system, it has been claimed that its use with other serotonergic agents may lead to serotonin syndrome. However, clinical studies are needed for this.

Phentermine/Topiramate

It was approved in 2012 for the long-term treatment of obesity. However, the EMA did not allow this combination due to the lack of long-term study data on topiramate's significant cardiovascular adverse effects, cognitive side-effect problems and the potential for abuse. [9] The mechanism of appetite suppression of this combination is not completely clear. Voltage-gated ion channel modulation, GABA-A receptor activity increase, and AMPA/Kainate glutamate receptor inhibition are thought to be effective in topiramate-induced appetite reduction. [10] Clinical studies show that topiramate can also inhibit compulsive eating and addictive behaviors. Topiramate, a GABA receptor activator, glutamate receptor inhibitor, and inhibitor of carbonic anhydrase enzyme, is also allowed for the epilepsy management and prevention of migraine attack. Significant weight reduction was seen in epileptic individuals managed with topiramate, which led to clinical studies for the obesity management. Phentermine is a noradrenergic agonist. Its central sympathetic effect occurs by increasing the norepinephrine, dopamine and serotonin release. It has been placed on the list of 4 drug groups by the FDA. This means a lower potential for abuse compared to list 3, which includes codeine and hydrocodone-like drugs. 11

EQUIP (n = 1267) and CONQUER (n = 2487) clinical studies were conducted to examine the effect of the combination of phentermine and topiramate on weight loss. The EQUIP study included non-diabetic volunteers with a BMI ≥ 35 kg/m^2, while the CONQUER study included volunteers with a BMI be-

tween 27-45 kg/m^2 and more than two obesity-related comorbidities. In the EQUIP study, the mean annual weight loss for individuals given the combination therapy was 10.9% (1.6% in the placebo group) versus 9.8% in the CONQUER study (1.2% in the placebo group). Improvements in cardiovascular system parameters were observed in both studies. A 2-year extension study, the SEQUEL study, was planned to evaluate sustained weight loss after these studies. The findings here supported the previous findings and showed that using phentermine/topiramate resulted in significant weight loss in the waist circumference by improving fasting insulin, fasting glucose, lipid profiles and blood pressure.

Common adverse effects of the combination are dry mouth, taste disturbance, constipation, dizziness, paresthesia, and insomnia. The drug can be taken in the morning to prevent insomnia. Although there is a structural similarity between phentermine and amphetamine, phentermine has no addictive potential and no risk of abuse. Even with prolonged use, amphetamine-like withdrawal is not observed when abruptly discontinued. [12] Birth control is recommended for women of childbearing age as it increases the risk of cleft palate.

Naltrexone/Bupropion

The FDA approved it in 2014 for a long-term weight loss treatment. Its mechanism is not fully understood. Naltrexone, bupropion, and dual combinations are thought to increase hypothalamic proopiomelanocortin (POMC) neuron firing frequency. Thus, by increasing proopiomelanocortin (POMC) activity, they provide modulation of the hypothalamic melanocortin system (homeostatic system) and mesolimbic dopamine reward system (non-homeostatic system).

Bupropion is used in cessation of smoking. The mechanism for anorectic action is dopamine and norepinephrine reuptake inhibition. Bupropion's alleged mechanism of action is to fire neurons that secrete α-melanocyte stimulating hormone (α-MSH). α-MSH reduces calorie intake and increases calorie consumption via MC4Rs (Melanocortin-4 Receptor). β-endorphin, a μ-opioid receptor agonist, is released in POMC neurons under physiological conditions, which inhibits the over-release of α-MSH. In this way, a negative feedback system works. Naltrexone inhibits β-endorphin-related negative feedback by blocking μ-opioid receptors, and this increase on POMC activity may be cause of its body weigtht reduction effects. Naltrexone is a drug used to treat opioid addiction. They create a synergistic effect with bupropion. [3]

The bupropion/naltrexone combination has been studied in different clinical studies COR-I (n = 1742), COR-II (n = 1496) and COR-BMOD (n = 793). Patients with diabetes, weight-related comorbidities, and patients with BMI ≥ 27 kg/m^2 were included in the 56-week studies. In the COR-I, COR-II, and COR-BMOD studies, weight loss in subjects given the 32/360 mg combination therapy was 6.1%, 6.4%, and 9.3%, respectively (1.3%, 1.2%, and 5.1% on placebo, respectively). The last study to evaluate weight loss in 505 overweight or obese diabetic patients is the COR-DM study. In this study, 5% weight loss was also observed in patients treated with a combined dose of 32/360 mg for 56 weeks (1.8% in the placebo group). In addition, HbA1c values also decreased from baseline. [13] In these studies, the bupropion/naltrexone combination improved lipid parameters in patients. Common adverse effects were headache, dizziness, gastrointestinal problems and dry mouth. The dose is gradually increased to prevent nausea. Blood pressure and heart rate may increase. There is a black box warning of an increased risk of suicidal thoughts and neuropsychiatric symptoms associated with this combination.

Liraglutide

Liraglutide is a derivative of glucagon-like peptide-1 (GLP-1) administered parenterally (3 mg/day subcutaneously). It was allowed by the FDA for type 2 DM in 2010 and for weight management in 2014. GLP-1 is released from the vagal nucleus of the solitary system, the proximal colon, and the distal ileum. It shows the effect of incretin after meals. GLP-1 shows its effect on blood sugar by increasing insulin level from principal beta cells of pancreas and reduces glucagon level in a glucose associated trait. [14] It also causes of postprandial satiety and fullness by showing ıts effects on the limbic/reward system, hypothalamus and cortex, slows gastric emptying, reduces appetite and food consumption. Liraglutide is strongly bound to plasma proteins and more stable in plasma. Thus, it provides a higher half-life (13 hours after a single injection) than endogenous GLP-1. [15] Liraglutide was approved after three large randomized controlled clinical trials: SCALE Diabetes, SCALE Maintenance, and SCALE Obesity/Prediabetes. [16] In the SCALE Obesity/Prediabetes study of 2487 obese volunteers, 61.2% of the participants were prediabetic. In the 56-week study, given liraglutide 3 mg 4 times daily or placebo, weight loss was 8% in the liraglutide group (2.6% in the placebo group). Of the patients given li-

raglutide, 63.2% lost ≥ 5% of their weight, and 33.1% lost ≥ 10%. The drug group's cardiovascular system parameters (blood pressure and lipids) were better. In addition, significant decreases were found in HbA1c and fasting blood sugar. [17] In the SCALE Diabetes study, 846 patients with type 2 DM who were overweight or obese were given liraglutide or a placebo at two different doses (3 mg 4 times a day or 1.8 mg 4 times a day) for 56 weeks. A 6%, 4.7% and 2% decrease was observed in the patient's weight, respectively. [18] The SCALE Maintenance study evaluated weight control in non-diabetic subjects on a low-calorie diet for four weeks. Four hundred twenty-two participants with 5% or more significant weight loss were randomized to subcutaneous 3 mg liraglutide/day or placebo. An additional 6.2% weight loss was observed in the drug group, compared to 0.2% in the placebo group. In addition, the improvement in cardiovascular parameters was remarkable in obese patients with type 2 DM. [19]

GLP-1 receptor analogues can increase amylase and lipase in a dose-independent manner, which raises concerns in terms of acute pancreatitis. However, it is stated that this risk does not increase significantly in long-term studies. In experimental studies, it is stated that liraglutide may be risky in patients with a predisposition for thyroid carcinoma. However, the findings of a long-term clinical study did not find a significant difference between liraglutide (≤ 1.8 mg/day) and placebo in terms of calcitonin levels and medullary thyroid carcinoma rates. [20] Although the optimal dose of liraglutide for weight loss is 3 mg per day, treatment should be started with 0.6 mg, and the dose should be increased gradually to avoid gastrointestinal complaints. A recent meta-analysis showed that liraglutide had the highest discontinuation rate due to adverse effects among all FDA-approved obesity drugs (13% of patients). [21]

COMBINED ANTI-OBESITY DRUGS

Due to the multifactorial factors in the development of obesity, a single anti-obesity drug may not show sufficient efficacy in the treatment or it may be necessary to increase the doses of the drug that cause unacceptable side effects. Anti-obesity drug combinations; It aims to increase to maximum the effect on weight, while being complementary, safe and tolerable. However, to date, there is no allowed combination drug for obesity treatment other than topiramate/phentermine and bupropion/naltrexone. Firstly, most of the combinations aims to controlling hunger/appetite/satiety with decreasing peripheral calorie absorption.

Sodium-glucose-co-transporter 2 (SGLT-2) inhibitors have been approved by the FDA for use with diet and exercise to lower blood sugar in type 2 diabetics. Drugs in this group include canagliflozin, dapagliflozin, and empagliflozin. These drugs inhibit renal glucose uptake and increase urinary glucose excretion. They are mainly used to regulate the blood sugar of people with DM. Interestingly, the efficacy of these agents in people without a diagnosis of diabetes is limited. While 8 kg of weight loss was observed in patients with diabetes for more than one year, in another study only 2 kg of weight loss was observed in diabetics. It has been claimed that this is due to compensatory eating behaviour and increased appetite. Based on this information, a combination of an appetite suppressant such as phentermine and an SGLT2 inhibitor drug might be reasonable for weight management. Indeed, significant weight loss was observed in clinical studies examining the combination of canagliflozin and phentermine. The weight loss observed with the combination therapy was 6.9%, compared to 1.3% with canagliflozin alone and 3.5% with phentermine alone. In another recent study, combination therapy was more successful than the use of drugs alone. [16]

The anorectic efficacy and safety of the combination of topiramate and diethylpropion were investigated in experimental studies. The drugs were given alone or in combination at dose ratios of 1:1, 1:3, and 3:1. The ED30 of these combinations is significantly higher than the experimental ED30 of non-deprived or 12-hour food-restricted mice. Interaction indices and confidence intervals also confirmed the possible potential between these two drugs. The theoretical ED30 value of this combination did not affect blood pressure. The data showed that low doses of the diethylpropion+topiramate combination deserve further study in clinical trials. The anorectic effects of these drugs appear to be potentiated with safer doses. [22]

Table 1 presents clinical studies on the safety and efficacy of FDA-approved anti-obesity drugs currently in use. Table 2 summarises the safety profiles of FDA-approved anti-obesity drugs currently in use.

TREATMENT PRINCIPLES IN OBESITY DRUGS

Despite accessibility, anti-obesity drugs are not used enough by healthcare workers. Just 2 percent of obese people eligible for obesity drug therapy receive

Table 1. Currently Used FDA-Approved Anti-Obesity Drugs and Efficacy Trials

Anti-Obesity Drugs	Clinical trials	Patient (n)	Clinical Trial Duration	Weight Loss
Orlistat		3305	4 years	%2,4
Lorcaserin	BLOOM	3182	2 years	> %10
	BLOSSOM	4008	52 weeks	> %10
Phentermine / Topiramate	EQUIP	1267	1 year	%10,9
	CONQUER	2487	1 year	%7,8
	SEQUEL		2 years	
Bupropion / Naltrexone	COR-I	1742	56 weeks	%6,1
	COR-II	1496	56 weeks	%6,4
	COR-BMOD	793	56 weeks	%9,3
	COR-DM	505	56 weeks	%5
Liraglutide	SCALE Obezite ve Prediyabet	2487	56 weeks	%8
	SCALE Diyabet	846	56 weeks	%6
	SCALE Maintenance	422	4 weeks	%6,2

a prescription from doctors. It is high ratio stigmatized disorder, there is a misunderstood that obesity is caused by a willpower deficiency and laziness. It is often thought that these patients do not deserve appropriate management with drugs or operation. The expensive prices of these drugs also blocks them from being adequately prescribed for long-term treatment. Achieving and maintaining weight loss is extremely difficult, and long-period treatment of obesity often needs additional pharmacological therapy options. In obese patients, it would be prudent to plan treatment by initiating drug therapy after a risk/benefit analysis. Consideration should be given to the growing evidence that these agents may delay the onset of obesity-related morbidities and achieve better metabolic and cardiovascular outcomes. More importantly, these drugs' risk/benefit ratios should be evaluated individually for each patient. Management strategy should be clear and unambiguous. Patient compliance affects the treatment and may even lead to the termination of the treatment. At each examine, physicians should evaluate the adverse effects associated with a particular agent and evaluate the agent's weight reduction effect.

The main management goal with an obesity drug in obese people should be permanent weight loss and improvement in general health. Physicians should convey these important messages to their patients when medication is started. Firstly, not every agent can cause efficient results in individuals, and wide variable responses can be seen. Secondly, when the maximum therapeutic effect of a agent is seen, weight loss reaches a plateau and then weight gain should normally be expected when drug therapy is discontinued. Management results of these agents should be considered for approximately 12 weeks usage of maintenance dose. 3-4 months trial period is needed to predict whether a person will observe significant weight reduction in one year. Lastly allowed anti-obesity drugs have FDA and EMA-recommended "Stop Rules" to help physicians identify individuals who can see > 5% weight loss within one year. Stopping rules can prevent harmful usage of drugs and increase the benefit/risk ratio. If, after 12 weeks, there is less than 5% weight loss with full-dose therapy (less than 4% weight loss in 4 months for liraglutide), the drug should be discontinued, and treatment with other medications should be initiated. However, it can be difficult for the physician to decide which obesity medication to continue after 12 weeks of full-dose therapy. In addition, only drug therapy is not considered when determining the withdrawal rules. All these are considered together, including anti-obesity medications and drastic lifestyle changes. Drug administration without calorie restriction and increased energy expenditure may result in less than 5% body weight loss after 12 weeks. [3, 11, 16]

ANTI-OBESITY DRUGS CURRENTLY UNDER RESEARCH

Melanocortin receptor (MC4R) agonists (Setmelanotide)

Known about the melanocortin receptor agonists (RM-493, BIM-22493, IRC-022493), which reg-

Table 2. Safety Profiles of Currently Used FDA-Approved Anti-Obesity Drugs (modified fromSrivastava G &Apovian C, 2018)

Anti-Obesity Drugs*	Contraindications	Warnings and Precautions	Advers Effects
Phentermine	Cardiovascular disease, the use of MAO inhibitor in 14 days, hyperthyroidism, glaucoma	Rarely primary pulmonary hypertension cases, increase in heart rate and blood pressure	Insomnia, dry mouth, constipation, agitation
Orlistat	Chronic malabsorption Syndromes, cholestasis	Decrease in vitamin absorption (multivitamin supplementation recommended)	Diarrhea
Phentermine / Topiramate	Glaucoma, hyperthyroidism, use of MAO inhibitor in 14 days	Fetal toxicity, metabolic acidosis, cognitive disorder	Paresthesia, dizziness, taste disorder, insomnia, constipation and dry mouth
Lorcaserin	Pregnancy	Risk of reaction like serotonin syndrome and neuroleptic malignant syndrome (medication is discontinued if there are symptoms of valve disease	In non-diabetic patients: headache, dizziness, fatigue, nausea, dry mouth and constipation and diabetic patients: hypoglycemia, headache, back pain, cough and fatigue
Bupropion / Naltrexone	Uncontrolled hypertension, seizures, anorexia nervosa or bulimia, chronic opioid use, simultaneous use with MAO inhibitors in 14 days	Suicide behavior and thought, increase in heart rate and blood pressure, hepatotoxicity, narrow angle glaucoma	Nausea, constipation, headache, vomiting, dizziness, insomnia, dry mouth and diarrhea
Liraglutide	Medullary carcinoma or Multiple endocrine neoplasia in personal or family	Thyroid C-cell tumors seen in rats and mice; Rarely, acute pancreatitis, acute gallbladder disease, renal failure, increase in heart rate, suicide tendency and behavior, serious hypoglycemia when used in insulin	Nausea, hypoglycemia, diarrhea, constipation, vomiting, headache, decrease in appetite, indigestion, fatigue, dizziness, abdominal pain and lipase increase

* All anti-obesity drugs are contraindicated during pregnancy

ulates eating behavior and feeling of fullness in the brain and affects insulin sensitivity, was advanced in 1992 with the POMC mRNA melanocortin peptides discover and the melanocortin cloning. Again, it has been clearly demonstrated that MC4R loss-of-function variants, which are highly prevalent in the Pima Indian population, cause energy dysregulation that causes monogenic type 2 DM and obesity. Compared to the MC4R gene, the MC3R gene is more critical in maintaining energy balance and foraging behavior after food deprivation. [23, 24] The effects of setmelanotide (infused continuously at 1 mg/day for 72 hours) on resting energy use in obese subjects were studied in a clinical study. [25] Male and female patients with a mean body mass index of 35.7 ± 2.9 kg/m^2 were evaluated with diet and half-hour physical activity once a day. While the resting energy expenditure of the patients increased by 6.4% compared to the placebo, wherewithal, the total daily energy expenditure increased, and the respiratory coefficients decreased. No side events were observed on blood pressure or heart rate. In another crossover study, setmelanotide treatment was associated with increased serum fasting glucose, triglyceride, free fatty acid, insulin, C-peptide, peptide YY, and total glucagon-like peptide-1. [26] Although MC4R activators have previously been observed to raise blood pressure and heart rate, no side events on blood pressure or heart rate have been seen. Other transient side effects include arthralgia, nausea, headache, female genital tenderness, and spontaneous penile erection. While cetmelanotide is currently allowed for some rare genetic diseases of obesity, it continues to be evaluated in others. These diseases include POMC deficiency obesity (FDA approval in

2020), LepR deficiency obesity (FDA approval in 2020), proprotein convertase subtilisin / kexin type-1 (PCSK1) deficiency (FDA approval in 2020), Bardet -Biedl syndrome, Prader-Willi syndrome (FDA approval in 2022), POMC heterozygous deficiency obesity, Alström syndrome, and POMC epigenetic diseases (FDA approval in 2022). Setmelanotide also has potential as replacement treatment for genetic obesity disorders like MCR4 pathway deficiences.

Neuropeptide Y Antagonist (Velneperit)

Velneperit (S-2367) blocks the binding of Neuropeptide Y (NPY) to Y5 receptors. Thus, it reduces hunger and strengthens the feeling of satiety. It was considered an anti-obesity drug because of its effect on hunger. But, it was abandoned for further studies after disappointing results in phase II clinical trials that showed moderate weight loss. [27, 28] Patients on a restricted calorie diet (RCD) or a low-calorie diet (LCD) were given two different doses of the drug (800 versus 1600 mg) in combination. The efficacy and safety of the drug were studied versus placebo in 1566 obese patients. Patients taking 800 mg of the drug lost an average of 3.8 kg. 35% lost more than 5% of their initial body weight. A weight loss of 7.1 kg was observed in the LCD trial in those who were given 1600 mg of medication for 54 weeks. 52% of these patients lost more than 5% of their baseline body weight. Results from the trial reported that velneperitin met the primary goal for weight reduction endpoints and the secondary endpoints of improvement and reduction in total lipid parameter. [2]9 However, Y5 receptor antagonists are considered to have the potential to be successful as an anti-obesity agent. A new combination drug of velneperit and orlistat is currently under investigation in different clinical trials.

Zonisamid/Bupropion

In many clinical studies, this combination has been shown to cause weight loss. Zonisamide is an antiepileptic used in the treatment of partial seizures. It blocks sodium and calcium channels, inhibits carbonic anhydrase enzyme, and has a dopamine-serotonin transmission effect. The known side effect of antiepileptic therapy is weight loss in patients. Bupropion is a dopaminergic agent and allowed for the management of smoking cessation and depression and provides weight loss when used as monotherapy because it reduces appetite. The depression-sedation effects and antiepileptic properties caused by zonisamide, when combined with the proconvulsant and anti-depressive effects of bupropion, form a complementary combination. [29] A pilot trial of 18 obese women demonstrated that the combination was superior to monotherapy. The mean weight loss of the combination of zonisamide and bupropion was 7.2 kg (7.5%) and 2.9 kg (3.1%) at 12 weeks against to placebo, respectively. %44 of the zonisamide administered monotherapy group dropped out because of poor tolerance and adverse events against to the combination therapy group with percentage of. [22] In a 24-week phase IIb study involving 729 obese patients given the combination of zonisamide and bupropion, more significant weight loss was observed in patients receiving the combined drug treatment than in monotherapy of both drugs and placebo. The proportion of subjects who lost more than 5% of their baseline body weight was approximately half of the patients in the bupropion (360 mg) + zonisamide (120 mg) combination and 60% of the patients in the bupropion (360 mg) + zonisamide (360 mg) group. The most commonly reported adverse effects were headache, insomnia, and gastrointestinal complaints. There were no differences in cognitive disorders, depression, anxiety, and suicidal ideation between the placebo and treatment groups. Phase II trials of this combination therapy have been completed, and phase III trials have been initiated.

Type-1 Cannabinoid Receptor Inhibitors

Stimulation of cannabinoid type-1 (CB1) receptors enhances orexigenic signaling, while antagonism of CB1 receptors inhibits food intake by activating anorexigenic signaling. Rimonabant (also known as SR141716) and AM251 are CB1 receptor antagonists/inverse agonists and have increased body weight reduction in experimental studies. [30] These former CB1 therapeutic antagonist aims also have the potential for centrally mediated effects. Rimonabant causes mood disturbances in 10% of patients and suicidal thoughts in approximately 1%. Other expected adverse effects include gastrointestinal complaints, flu symptoms, upper respiratory tract infections, anxiety, nervousness, sleep problems, hot flashes, dry skin, tendinitis, muscle cramps and spasms, and fatigue. Side effects such as similar symptoms and raised risk of falls have been reported. Clinical studies and post-marketing surveillance data have shown a double risk of psychiatric problems such as depressive disorders, anxiety and thoughts of suicide in people taking rimonabant. Due to these risks, rimonabant was withdrawn from the stores in 2009. [31, 32]

Semaglutide and Other Oral GLP-1 Agonists

GLP-1 receptors are found in the brain. They can directly affect various neural circuits, including GLP-1 signals from the periphery to regulate calorie consumption and weight maintenance. [33] Liraglutide is a GLP-1 analogue used parenterally (3 mg/day subcutaneous injection). It is approved for the treatment of obesity. This drug is effective in obese and type 2 diabetic patients. However, its extended-release pharmaceutical form is still not approved for treating obesity. Semaglutide (NN9536), a long-acting GLP-1 analogue, is currently being studied. Clinical data both in treating obesity and in people with type 2 diabetes are promising. At the end of 3 months of treatment, the energy intake of patients given subcutaneous semaglutide once weekly decreased by 24%, and their body weight decreased by 5 kg. [34] In clinical trials evaluating the effects of once-weekly use in type 2 diabetics, a decrease in HbA1c and weight loss were observed. Its safety profile is similar to other GLP-1 receptor activators. The main adverse effects observed with these drugs are gastrointestinal complaints. There was no increased risk of pancreatitis and pancreatic cancer in controlled clinical trials. However, caution should be studied regarding cholelithiasis. [35] Other minor GLP-1 activators, such as TTP054/TTP-054 and ZYOG1, which can be administered orally, are being investigated as an alternative to parenteral drugs with low side effects. [36]

Amylin Mimetics and Dual Amylin-Calcitonin Receptor Agonists

Amylin is a pancreatic beta-cell hormone. It creates a central effective satiety signal, reducing calorie consumption by affecting the area postrema, where the peripheral peptide signal may directly connect with cerebral neurons. It also increases gastric motility and reduces postprandial glucagon release. The area postrema also connects to the nucleus solitarius and other brain autonomic control centers. As a result, amylin signaling shows a regulator effect over energy metabolism by reducing the orexigenic neuropeptides expression. Subtypes of human amylin receptor are complexed with receptor activity-modifying proteins of the calcitonin receptor. [37] Due to their mechanism of action, amylin mimetics coupled with dual-acting amylin and calcitonin receptor activators (also known as DACRA) have emerged as promising new anti-obesity drug target. Davalintide (AC2307), an amylin-mimetic peptide, decreased calorie consumption and weight with increased metabolism on amylin in animal trials. [38, 39] In last trials, DACRA (KBP-088 and KBP-042) achieved superiority against to davalintide in efficacy for in vitro receptor pharmacology, in vivo calorie consumption, and weight loss. [40] DACRA improved oral glucose tolerance and hyperinsulinemia in rats fed a high-fat diet. It also reduced adipose tissue cell hypertrophy, resulting in weight loss. A long-acting amylin analogue given once daily is being tested in phase I clinical trial.

Glucose Linked Insulinotropic Polypeptide (GIP) Analogue

Gastric Inhibitory Peptide is a polypeptide hormone consisting of 42 amino acids. However, inhibition of gastric secretion could not be confirmed in subsequent human studies. The fact that it shows a glucose-dependent insulinotropic effect in further studies suggests a role of incretin. GIP shows effect on stabilizing blood sugar levels, in contrast to glucose associated effects on insulin and glucagon release, respectively. [41] High-level GIP signaling in adipocytes can lead to lipid deposition, hepatic steatosis associated with visceral fat deposition, and insulin resistance. In animal trials, the GIP analogue ZP4165 did not change body weight in obese subjects, similar to the GLP-1 receptor activators, although it exerted an insulinotropic effect in rats and decreased HbA1c levels in diabetic mice. GLP-1-induced significant weight loss suggests that the combined treatment of GIP and GLP-1 agonists should be further studied instead of GIP monotherapy in treating obesity and diabetes. [42]

Dual Action GLP-1/Glucagon Receptor Agonists, GC-CO-Agonist 1177, and Triple Agonist Glucagon-GIP-GLP-1 Agonist (Tri-agonist 1706)

For over 50 years, glucagon has been known to reduce food intake and increase human satiety. Further studies investigating the use of GLP-1 receptor activator and glucagon combinations (Oxyntomodulin, MEDI0382, G530S (Glucagon analogue+semaglutide)) revealed that glucagon reduces hunger by neuronal stimulation in the area postrema and central nucleus. [43] Oxyntomodulin is a dual receptor activator peptide of GLP-1/glucagon and secreted by endocrine enteral L cells and is reduce hunger, reduce calorie consumption, and raise energy consumption. Overweight and obese subjects have been seen to decrease body weight by 2.3 ± 0.4 kg in the management group over the trial time against to the control group following 4 weeks of management. [44] Tirzepatidine, a novel glucose-dependent insulinotropic polypeptide,

and GLP-1 agonist, achieved a significant and sustained reduction in body weight in an approximately 1.5-year clinical trial in 2539 obese patients (dosed at 5 mg, 10 mg, or 15 mg/week). Further studies of its efficacy and safety in obese individuals are planned. [45]

Peptide YY (PYY)

It is secreted from L cells of the colon and ileum in response to food intake and has anorexigenic effect. It is a 36 amino acid peptide with a U-shaped fold. [46] Its two main forms are PYY3-36 and PYY1-36. The most abundant biologically active form in the bloodstream is PYY3-36, which binds to the Y2 receptor (Y2R) of the Y receptor family and shows structural homology. PYY decreases gastric motility and increases satiety. It decreases appetite and food consumption through NPY receptor blockade. [47] Obese individuals have lower levels of PYY. In addition, the increase in PYY is blunted after satiety. Infusion of PYY has also achieved to decrease levels of the ghrelin which an oroxigenic hormone. [48] Failure to maintain high PYY levels also causes weight gain after bariatric surgery. [49] Although it is an important anti-obesity agent target to study, it has a few restrictions, firstly its short half-life that affects usage and stability. Phase I and II clinical trials are currently testing strategies to develop different pharmaceutical drug forms, such as long-acting subcutaneously administered analogs, oral-intravenous forms, and nasal sprays.

Leptin Analogues

Since animal studies of leptin, a hormone secreted by adipocytes, have linked leptin deficiency with severe obesity, it was initially considered a successful treatment for obesity. Conversely, however, obese people are leptin-resistant and have much more leptin levels. [50] Therefore, combination therapies have been tried to block leptin resistance. Metreleptin is a parenteral leptin analog. It corrects hyperglycemia and hypertriglyceridemia and reduces hepatic adiposity. It has been associated with lipodystrophic diseases that cause congenital or familial loss of adipocytes. It has been approved in Japan and the US for limited indications in individuals with lipodystrophy and leptin deficiency. Decreased treatment efficacy and weight regain after meterleptin treatment may be observed in patients. This has been attributed to the development of anti-metreleptin antibody immunogenicity. The most commonly expected drug-related adverse effects (≥ 10%) are headache, weight loss, hypoglycemia, and abdominal pain. T-cell lymphoma has occurred in individuals with acquired generalized lipodystrophy independent of metreleptin treatment.

Pramlintide is a synthetic analog of amylin peptide hormone with anorexigenic action. It reduces food intake, and weight gain is released in response to calorie consumption and has a glucose-regulating effect. It is approved for treating diabetes mellitus and reduces calorie consumption and weight in obese individuals regardless of diabetes. Pramlintide produces a shorter-lasting satiety signal in contrast to leptin. It has been shown to improve the leptin pathway in experimental studies. This suggested that the neurohormonal combination may have a synergistic or additive effect. In phase II clinical trials comparing the combination of pramlintide/metreleptin with monotherapies, more significant weight loss was achieved without any plateau phase being observed. In the 52-week extension study of this trial, weight loss continued in the treatment group, while the placebo group regained all lost weight. [11] The most seen side events are mild or moderate nausea that subsides over time.

OTHER PROMISING NEW DRUG TARGETS

Beloranib

This fumagillin analogue drug is a methionine aminopeptidase 2 (MetAP2) inhibitor that reduces the synthesis of new fatty acids in the liver and converts stored fat into usable energy.

It was first used as an anti-angiogenetic agent in cancer treatment. After the role of MetAP2 in obesity was understood, antiobesity effects started to be studied. Different doses of beloranib given parenterally twice a week resulted in significant weight loss compared to placebo. It also showed improvements in lipids, C-reactive protein, and adiponectin. In a phase II study investigating the tolerability and efficacy of the drug, it improved weight loss and cardiometabolic risk factors. [51] Although gastrointestinal side effects and sleep disturbances were reported most frequently in relation to beloranib, it was generally found to be safe and well tolerated. It has led to significant weight loss and hypophagia in experimental hypothalamic and genetic models of obesity. Due to patient deaths, the FDA halted a phase III clinical trial in Prader-Willi patients in December 2015. [52]

Lipase Inhibitor

Cetilistat (ATL-962) has a similar effect to orlistat. It is an inhibitor of pancreatic and gastric lipase.

Reduced weight gain and improved lipid parameters in diet-induced obese rats. In a multicenter, randomized, placebo-controlled, phase II parallel group trial, the cetilistat group significantly reduced mean body weight against to placebo, resulting in improvement in lipid profiles. Treatment-emergent side effects were similar between treatment groups. More gastrointestinal adverse events were reported in the cetilistat group against to placebo. [53] In another phase II clinical trial, cetilistat was better tolerated than placebo and orlistat groups, and fewer patients discontinued the drug due to adverse effects. Cetilistat shows more promise than orlistat due to milder potential gastrointestinal adverse events (such as diarrhea, bloating, and oily stools). [54]

Inhibitors of Triple Monoamine Reuptake

Tesofensine (TE) is a recently discovered potent triple monoamine (dopamine, norepinephrine, and serotonin) reuptake inhibitor. In animal models, it increased dopamine levels in the forebrain and induced weight loss in diet-induced obese rats. In a phase II study involving obese patients given TE at dosages of 0.25, 0.5, or 1 mg/day for 24 weeks, an average of 4.5%, 9.2%, and 10.6% more weight loss was observed than placebo, respectively. Clinical studies have shown that it is effective in the treatment of anti-obesity. It has similar pharmacological properties to sibutramine. Therefore, it can potentially increase heart rate, blood pressure, and psychiatric disorders, and further studies on its safety are needed. [55]

Fibroblast Growth Factor (FGF) 21

It is a member of the FGF family, produced in the liver but can also be released from adipocytes, skeletal muscle, and the pancreas. It regulates metabolism by promoting both weight loss and glycemic control. [56] While the molecule acts on multiple organs, it is a triple autocrine, paracrine and endocrine factor. FGF21 stimulates uptake of glucose and release of adiponectin by transforming sensitive white adipocytes stores into brown adipose tissue. Activates both uptake of glucose and thermogenesis in brown adipose tissue. Its ability to raise energy consumption makes it a potential drug target for obesity. Reduces hepatic growth hormone signaling and regulates fatty acid oxidation. In experimental studies, it preserved lipid homeostasis in both fasted, and mice fed a low-carbohydrate and high-fat ketogenic diet. It is also known to have anti-inflammatory, anti-oxidative stress effects related to increased levels of this molecule during muscle-related or critical stress periods. [57]

Obesity Vaccines (Ghrelin, Somatostatin, AD36)

While the focus has so far been on anti-obesity agents that directly or indirectly increase anorexigenic signals, vaccines are a potential new therapeutic approach to prevent or treat obesity. The main point in the producing of obesity vaccines is to decrease appetite activating hormones and/or prevent food intake. Ghrelin has an important vaccine potential. Experimental data have shown that the anti-ghrelin vaccine reduces calorie intake, increases calorie utilization, and reduces hypothalamic orexigenic stimulation. In clinical trials, a strong response in ghrelin autoantibodies was achieved after four different doses of the anti-ghrelin vaccine. However, despite all these, the lack of significant weight loss has lowered hopes. [11] Somatostatin hormone inhibits insulin-like growth factor-1 and growth hormone (GH) release. Decreased basal GH release is associated with obesity and adiposity. Somatostatin vaccination aims to counteract the inhibitory effects of somatostatin and increase endogenous GH and immunoglobulin levels. Experimental studies showed a 10% reduction in body weight gain due to vaccination despite a fatty diet, while food intake remained unchanged. [58] Adenovirus 36 (AD36) has been shown to affect obesity risk in humans, increasing inflammation and adiposity. In mice injected with the AD36 vaccine, inflammatory cytokines and macrophages in adipose tissue were reduced after 14 weeks compared to the control group. In addition, more than a 17% reduction in body weight and more than 20% reduction in the epididymal fat increase were observed in the vaccinated group. Virus-induced vaccine prophylaxis may become an important treatment management target against obesity in the near future. [59]

The pharmacological profiles of novel drugs and drug-target agents currently under development are summarized in Table 3.

CONCLUSION

In the treatment management of obese patients, given the enormous costs and high burden of disease, current pharmacologic treatment options are not sufficient to meet clinical heterogeneity. Despite this shortcoming, anti-obesity drug studies and currently approved anti-obesity drugs give hope to the medical community. In this respect, it is important to increase medical options for obesity treatment with more effective management strategies. With the increase in

Table 3. New Drugs Currently in Development and Drug Targets (modified from Srivastava G & Apovian C, 2018)

Anti-Obesity Drugs	Other Names	Mechanism of Action	Effects	Adverse Effects	Clinical Benefits
Setmelanotide	RM-493 BIM-22493 IRC-022493	MC4R agonism	Decreased body weight, increased energy consumption	Headache, arthralgia, nausea, spontaneous penile erections, female genital area sensitivity	Trial for rare genetic diseases
Bupropion / Zonisamide	Empatic	Combination of a dopaminergic agent with an antiepileptic that provides sodium and calcium channel blockade, carbonic anhydrase inhibition and dopamine-serotonin transmission	More significant weight loss than monotherapy, stabilization of depression and proconvulsant effects with combination therapy	Nausea, headache, insomnia	Phase II trials completed
Cannabinoid type-1 receptor blockers	SR141716, AM251, AM6545	Cannabinoid type-1 receptor antagonism: anorexigenic signal attenuates	Weight loss in experimental studies	Depression and mood swings	
Semaglutide	NN9536; oral GLP-1 agonists: Semaglutid, TTP054/TTP-054 and ZYOGI	GLP-1 agonism	Decreased HbA1c, weight loss	Safety profile similar to GLP-1 agonists, fewer hypoglycemic events	Type-2 DM, obesity
Amylin mimetics	Davalintide (AC2307), KBP-088, KP-042 (dual amylin and calcitonin receptor agonists)	Pancreatic β-cell hormone (generates a central satiety signal that reduces food intake, slows gastric emptying, reduces satiety glucagon secretion); human amylin receptor subtypes are complexes of the calcitonin receptor	Reduces food intake and body weight improves oral glucose tolerance	Hypoglycemia	Type-2 DM, obesity

Table 3. (continued)

Anti-Obesity Drugs	Other Names	Mechanism of Action	Effects	Adverse Effects	Clinical Benefits
Velneperit	S-2367	Noropeptide Y5 receptor antagonist	Anorexia	Discontinued due to insufficient weight loss in phase II clinical trial	
Glucose-dependent insulinotropic polypeptide analogues	ZP4165	Increased GIP signalling in adipose tissue-induced insulin resistance, lipid storage and hepatic steatosis; GLP-1-induced weight loss enhancement by the combination of GLP-1 agonist and GIP	Insulinotropic effects and reduced HbA1c levels in diabetic mice, no effect on weight loss		Type-2 DM, obesity
	Pramlintide-Metreleptin	Synthetic analog of amylin peptide combined with the leptin analog; pramlintide is approved 30ort he treatment of type- 1 or 2 DM	Reduced food intake, with an average weight loss of 11% in combination trials	Mild-moderate nausea	Type-2 DM, obesity
Dual action GLP-1/glucagon receptor antagonist	Oxyntomodulin(OXM), MED10382, G530S (glucagon analogue + semaglutide), GC-co-agonist 1177	Glucagon monotherapy is hyperglycemic, but combining GLP-1 agonist and glucagon induces anorexia	Appetite suppressed, food intake reduced, and energy consumption increased	The short duration of action, limited clinical benefit	Long half-life drug development studies
Peptide YY	PYY	Decreases gastric motility, increases satiety, inhibits NPY receptors	Decreases appetite and food intake	Short half-life and stability limit the clinical utility	PYY infusion reduces the orexigenic hormone ghrelin levels. A blunt increase in postprandial PYY levels is associated with lower PYY levels in obesity

Table 3. (continued)

Anti-Obesity Drugs	Other Names	Mechanism of Action	Effects	Adverse Effects	Clinical Benefits
Leptin analogues	Metreleptin	Human recombinant leptin injectable analog	Improves hyperglycemia and hypertriglyceridemia, reduces hepatic fatty steatosis	Common adverse effects are headache, hypoglycemia, weight loss and abdominal pain.	Approved in Japan for lipodystrophic disorders, in the USA for non-HIV generalized lipodystrophy
Beloranib		Fumagillin analogue that inhibits methionine aminopeptidase 2 (reduces new fatty acid molecules in the liver, converts stored fat into usable energy); a novel angiogenesis inhibitor	It induced potent weight loss and hypophagia in 31ouse hypothalamic and genetic models of obesity. It also showed improvements in lipids, C-reactive protein, and adiponectin in clinical trials	Sleep disturbance and gastrointestinal side effects	Phase III clinical trial in Prader-Willi patients terminated in 2015 after 2nd patient's death
Lipase inhibitor	Cetilistat (ATL-962	Inhibitor of pancreatic and gastric lipase	Improved lipid profile and weight loss	Gastrointestinal side effects are better tolerated than orlistat	Obesity, hyperlipidemia, prediabetes, DM
Anti-Obesity vaccines	Ghrelin	An orexigenic hormone secreted by gastric fundus cells	Decreased food intake, decreased hypothalamic orexigenic signalling and increased energy expenditure in experimental studies	No weight loss in clinical trials	
	Somatostatin	Peptide hormone which inhibits growth hormone and insulin-like growth factor 1 secretion (IGF-1)	Decreased GH secretion is associated with obesity and increased adiposity. The somatostatin vaccine can eliminate the inhibitory effects of somatostatin and increase endogenous GH and IGF-1 levels	Vaccination did not affect changes in food intake in experimental studies	
	Adenovirus 36 (AD36)	Associated with obesity, inflammation, and increased adiposity	Vaccinated mice showed a more significant reduction in body weight and a reduction in inflammatory changes in adipose tissue in experimental studies		

the knowledge of the disease process, it will be possible to achieve new successes regarding these drugs and to approach this complex disease more rationally from a therapeutic point of view.

Authors' Contribution

Study Conception: PT, IY, HY,; Study Design: PT, IY, ID,; Supervision: IY, HY, ID,; Literature Review: PT,HY,; Manuscript Preparation: PT, HY, IY and Critical Review: IY, ID.

Conflict of interest

None to declare

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Initial values of skeletal muscle parameters in patients presenting with acute pancreatitis

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ABSTRACT

Objectives: Predicting the clinical course of acute pancreatitis has been discussed previously on the basis of visceral adipose tissue. This study was conducted to determine the relationship between clinical outcomes of acute pancreatitis and changes in skeletal muscle parameters.

Method: This is a single-center, cross-sectional, retrospective study. Patients who were diagnosed with acute pancreatitis between 01-28 February 2019 and had abdominal computed tomography (CT) taken in the first week of their hospitalization were included in the study. L3 level of abdominal CT images were used to evaluate skeletal muscle parameters.

Results: During the hospital database scanning, 127 patients newly diagnosed with acute pancreatitis were included in the study. The median age was 50 (18-88) years, 47% were male, and 53% were female. The median body mass index (BMI) was 26,42 (19.4-46.8) kg/m2. Fifty-one % of patients were diagnosed with biliary acute pancreatitis, and 48.8% were diagnosed with non-biliary acute pancreatitis. At the same time, acute pancreatitis severity was classified according to revised Atlanta criteria, 67.7% were mild (n = 86), 28.3% were moderate (n = 36) and 5 (3.9%) patients were severe. Skeletal muscle mass was evaluated using the total psoas index (TPI) and, skeletal muscle density calculated by HU. Median TPI was 6.3 (2.5-13.7). The median of Hounsfield Unit (HU) average calculation was 18.9 (3.8-28.5) (Table 1). There were no statistically significant differences on sex, age, BMI, skeletal muscle parameters, and acute pancreatitis clinical outcome (Table 2).

Conclusion: Skeletal muscle parameters determined by TPI and HU were not a predictor of the clinical course, and viewing them always cannot be effective to investigate their effect on acute pathologies. So, this way couldn't be proposed as a perfect method for predicting clinical outcome of acute pancreatitis.

Keywords: skeletal muscle parameters, pancreatitis, computed tomography, L3 level

Acute pancreatitis is the most seen disease of the pancreas. The incidence varies between 13 and 45 per 100,000. [1] Acute pancreatitis is typically a mild disease, it can be severe at about 10%, and also the fatality rate is higher in these patients. [2, 3] Various scoring systems like acute physiology evaluation, age and chronic disease assessment II (APACHE-II) [4] or Ranson classification criteria have been developed to predict the prognosis in acute pancreatitis. [2, 3]

Visceral adipose tissue and skeletal muscle mass around pancreas can be affected by cytokines secreted

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in acute pancreatitis, and its damage is associated with the development of necrotizing pancreatitis. [5] Unsaturated fatty acids produced by adipose tissue in case of acute pancreatitis can cause inflammation, necrosis and organ failure. [6] This relation between the severity of acute pancreatitis, visceral adipose tissue, and muscle parameters are controversial; therefore, there has also been some study which has shown no association. [5, 6]

Skeletal muscle parameters can be evaluated by measuring psoas muscle area and muscle density using cross-sectional imaging (computed tomography) methods. [7] Mean skeletal muscle attenuation measured by HU is an indicator of skeletal muscle density (SMD). Low skeletal muscle density indirectly reflects increased intramuscular adipose tissue and low skeletal muscle quality. Skeletal muscle mass has been shown to affect cancer-related outcomes. Skeletal muscle mass has prognostic effects in patients treated with cancer treatments and is a general predictor of clinical outcomes. Also, skeletal muscle mass affects operative complications such as colectomy, hepatic and pancreatic resection. [8, 9, 10]
Atlanta criteria has been changed in 2012 for better clinical evaluation, and treatment of acute pancreatitis. Radiological scanning has become more important in the diagnosis and follow-up of patients with acute pancreatitis. [11, 12] The contrast-enhanced CT is the first step for the diagnosis and follow up of acute pancreatitis.

In many diseases, some body parameters are associated with the severity of clinical outcomes, but this cannot be said for severe and necrotizing pancreatitis. With this study we aimed to answer the question "is there a relationship between the severity of acute pancreatitis and skeletal muscle parameters?"

METHODS

Study design and patient selection

This is a retrospective single-center cross-sectional study. We do not need informed consent owing to its retrospective design. To establish a homogenous cohort, patients diagnosed with acute pancreatitis in our hospital between 01-28 February 2019 were identified by retrospective screening of the hospital database. The baseline characteristics on initial admission including age, sex, body mass index, etiology and medical records were obtained from the hospital database. Patients diagnosed with acute pancreatitis and abdominal CT taken within the first week after admission to hospital were included in the study. Axial CT images at L3 level were performed for calculation.

CT was taken by 16-slice CT scanner (Optima 520 CT, General Electric (GE) company). All images were used from Picture Archiving and Communication System (PACS), and reviewed by a trained radiologist who was blinded of patient outcomes. Measurement of the psoas muscle area was calculated from the L3 vertebra level by measuring with the free hand technique. The severity of pancreatitis was classified according to Atlanta criteria.

Evaluation of muscles parameters

Psoas area values were calculated based on height in the first method of cross-sectional imaging, and cm^2 / m^2 unit was used for total psoas index (TPI). TPI calculation formula was used according to patient height: [right psoas area + left psoas area] / [height2]. Gender-specific quarters were produced and taken as a cut off value for the lowest 25% undercut in each approach. Cut off was taken as 6.3 cm^2 / m^2 in men, and 3.9 cm^2 / m^2 in women for the TPI calculated from the L3 level. [5, 6, 7]

Determination of skeletal muscle density was obtained by measuring a mean skeletal muscle attenuation in Hounsfield Unit (HU). Low skeletal muscle density is equal to increased intramuscular adipose tissue and poor skeletal muscle quality. HU average is calculated by the following formula; [right average HU x right psoas area] + [left average HU x left psoas area] / [TPA]. [5, 6, 7] Gender-specific lower quarter was 17,4 for men and 14 for women.

Statistical analysis

SPSS for Windows (v. 22; IBM Corp., NY, USA) was used to analyze the data. While evaluating the data, descriptive statistics were evaluated as mean, standard deviation, median, frequency, and ratio. Pearson Chi-Square test, Mann–Whitney test, and General Linear Model were used to compare qualitative data. Statistical significance was predicted as $p < 0.05$.

RESULTS

During the hospital database scanning, 127 patients newly diagnosed with acute pancreatitis were included in the study. The median age was 50 (18-88) years, 47% were men, and 53% were women. The median body mass index (BMI) was 26,42 (19.4-46.8) kg/m^2.

Table 1. Baseline characteristics of all patients

Characteristics		*Statistics*	
Age, median in years		50 (18-88)	
BMI, median in kg/m²		26,42 (19.4-46.8)	
Sex	**Female n (%)**	60	47,2%
	Male n (%)	67	52,8%
TPI, median		6,3 (2,5-13,7))	
Pancreatitis type	**Biliary**	62	48,8%
	Non-biliary	65	51,2%
HUAC, median		18,9 (3,8-28,5)	
Atlanta classification	**Mild AP n (%)**	86	67.7%
	Moderate AP n (%)	36	28.3%
	Sever AP n (%)	5	3.9%

* Hounsfield Units Average Calculation (HUAC)= (right area x density) + (left area x density) / total area;
*Total Psoas Muscle Index (TPI)= (Total Psoas Muscle Area/ height square). *AP: acute pancreatitis

Most common etiologies were biliary 51%. Sixty-seven % were mild (n = 86), 28.3% were moderate (n = 42) and 5 patients were severe, according to Atlanta criteria at the time of admission. Skeletal muscle mass was evaluated using the total psoas index (TPI) and, skeletal muscle density calculated by HU. Median total psoas index (TPI) was 8,2 ± 2,1 in men, and 5,3 ± 1,4 in women. The median of Hounsfield Unit (HU) average calculation was 20,7 ± 4,2 in men and 17,3 ± 5 in women (Table 1). There was no statistical significance between acute pancreatitis clinical outcome and skeletal muscle parameters (Table 2).

DISCUSSION

The focus of our study was to find the answer of a question about the relationship between acute pancreatitis criteria and muscle condition, as well as to evaluate its effect on clinical outcomes. Severe pancreatitis rate was numerically lower, it should be noted that 2.4% of patients were necrotizing pancreatitis at the time of CT scanning on admission to the hospital.

In a prospective cohort study conducted in the Netherlands, a total of 496 patients with a diagnosis of necrotizing pancreatitis were evaluated. They investigated the effect of body composition on hospital mortality using the first CT images and found no significant correlation between severe necrotizing pancreatitis and muscle parameters. [5] Another retrospective study from South Korea evaluated body fat and muscle distribution on acute pancreatitis in 203 patients from 2009-2015. Six % of patients were diagnosed with severe and 30% were moderately acute pancreatitis. They measure the muscle parameters with abdominal CT at L3 vertebral level. In this study,

Table 2. Statistical analysis for risk factors for severe acute pancreatitis

	Univariate OR (95%)	P value
Sex		
Male	1,18 (0,4-3,53)	1,000
Female	0,87 (0,41-1,82)	
Age		
≥ 65 years	0,65 (0,21-1,99)	,610
< 65 years	1,23 (0,59-2,53)	
BMI		
≥ 30kg/m²	1,03 (0,2-5,24)	1,000
< 30	0,98 (0,43-2,2)	
Etiology		1,000
Biliary	0,84 (0,4-1,7)	
Non-biliary	1,23 (0.41-3,65)	
Skeletal muscle index (cm²/m²)	3,4 (0,5-21,6)	,334
Skeletal muscle density (HU)	0,74 (0,67-0,82)	,207

high visceral fat was strongly correlated with the severity of acute pancreatitis. 10 Multicenter study conducted by Sternby et. al. [13] retrospectively and consecutively enrolled 454 patients with acute pancreatitis at first contrast-enhanced CT evaluated and measured adipose and muscle tissue parameters at L3 level. They declare that decreased muscle mass level was associated with severe acute pancreatitis. [13]

A single center prospective study from USA investigated the conversion of acute pancreatitis to severe pancreatitis, over 10 years period between 2009-2019. The median age was 53 years, median BMI is 28.3, etiologies include was alcohol 34.4% and biliary 34%. Abdominal CT images from L3 level was chosen for measurement. In this study it was shown that pancreatic lipases are responsible for the development of severe pancreatitis with lipolysis of visceral adipose tissue, independent of necrosis and inflammation. [14] Another study from Turkey evaluated the abdominal fat distribution and severity of acute pancreatitis in total 174 patients between January 2015-December 2018. The mean age was 58, 61% (107) were female, 38% (67) were male. Eighty-one % of patients had mild and 19% had moderate acute pancreatitis diagnosis. Sixty-five % among all patients were diagnosed with biliary etiology. It was found that increasing the adipose tissue ratio, is associated with an increase in acute pancreatitis clinical scores. [15]

Our cross-sectional study aimed to detect a change in skeletal muscles as an indirect indicator of visceral adipose tissue, at the time of acute pancreatitis and its effect on clinical outcomes. Most of the files scanned retrospectively were diagnosed with mild and moderate acute pancreatitis, only 5 patients at the time of diagnosis appeared with necrotizing pancreatitis. Based on our results, there was no significant relationship between skeletal muscle parameters and acute pancreatitis clinical presentation.

Limitations of the study

Firstly, our study was a single-center retrospective observational study design, and all data are reflecting just a muscle functions not intramuscular fat accumulation. In the next studies, muscle mass, and muscle function should be evaluated together in result-based analysis. Secondly, the duration of follow up in our study was short, the number of cases of severe pancreatitis was small; therefore, we cannot say that is strictly unrelated.

CONCLUSION

Skeletal muscle parameters determined by TPI and HU is not an important predictor of the clinical course and viewing them cannot be effective to investigate their effect on acute pathologies. As a result of these studies, a perfect method for predicting severe acute pancreatitis couldn't be proposed.

Statement of ethics

The study is retrospective conducted we did not get informed consent from patients, and all procedures performed were part of routine care. Approved by the local ethics committee (approval#03.01.2019/032). The study was conducted in accordance with the Helsinki Declaration, and Good Clinical Practices guideline.

Author's contribution

Conceptualization: [Aysun Isiklar], Methodology: [Aysun Isiklar, Taha Yusuf Kuzan]; Formal analysis and investigation: [Aysun Isiklar, Taha Yusuf Kuzan]; Writing - original draft preparation: [Aysun Isiklar]; Writing - review and editing: [Aysun Isiklar, Taha Yusuf Kuzan]; Supervision: [Aysun Isiklar, Taha Yusuf Kuzan]

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Conflict of interest statement

The authors have no conflicts of interest to declare.

Data availability statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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The atherogenic index of plasma complicates the thrombotic tendency of chronic myeloproliferative disorders: A retrospective cohort study

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ABSTRACT

Objectives: Chronic myeloproliferative diseases (CMPD) are neoplastic disorders leading to hypercoagulability and thrombosis. The critical hemostatic abnormalities include alterations in the blood viscosity and a history of recent thrombus. The aim of this study is to assess the interrelationships among the atherogenic index of plasma (AIP) and thromboembolism of CMPD with JAK2 V617F mutation.

Methods: Ninety-two patients diagnosed as CMPD with JAK2 V617F mutation and 73 controls were included into the study. The patients were evaluated for the presence of any venous or arterial thromboembolic events. AIP was calculated by using the formula log (Tg/HDL) from serum triglyceride and high-density lipoprotein values.

Results: The study group consisted of 30 patients (33%) with myelofibrosis (MF), 42 patients (46%) with polycythemia vera (PV) and 20 patients (21%) with essential thrombocythemia (ET). Two study groups were similar in terms of sex, age and other comorbidities ($p > 0.05$). CMPD group had higher levels of right blood cell count (RBC), red blood cell distribution width (RDW), platelets (PLT), hemotocrit (Hct) and AIP. Univariate and multivariate logistic regression analysis revealed that platelet count, RBC and AIP were independent predictors for thrombosis in both groups. The comparison of ROC curve analysis disclosed that AIP was superior to platelet count and RBC in predicting thrombosis.

Conclusion: AIP can be used to determinate higher risk of thromboembolism in patients with CMPD. As a reliable and 'easy-to-assess' diagnostic tool, AIP could be useful for the determination of thrombotic events in CMPD clinicobiological disease course.

Keywords: Atherogenic index, myeloproliferative, Janus kinase, thromboembolism,

BCR-ABL negative chronic myeloproliferative diseases (CMPD) namely; essential thrombocythemia (ET), polycythemia vera (PV) and primary myelofibrosis (PMF) are driven by functional pathogenic mutation. [1, 2] The Janus kinase 2 (JAK 2) V617F mutation is the most common genetic mutation. It is detected in almost all of the patients with PV and about half of PMF and ET patient population. [3, 4] Numerous symptoms including fatigue, weight loss, loss of appetite, abdominal swelling, early satiety, rapid bleeding/bruising, painful joint swellings, tinnitus and pain radiating from the left upper quadrant to

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the left shoulder could be observed during the clinical course of CMPD, especially in MF. [5] Thrombotic and hemorrhagic anomalies are among the leading causes of the morbidity and mortality in all subgroups of CMPD. [6] Arterial and venous thromboses are associated with adverse outcome in PV. The symptoms of PV primarily occur due to elevated red blood cell count (RBC) which results in the increased blood viscosity and beyond this high platelet counts contribute to the occlusion of vessels. Thrombosis is responsible for 45% of the deaths in those patients with CMPD. [7-9] Thrombosis of the greater arteries is an important cause of mortality due to ET or can trigger severe neurological, cardiac or peripheral arterial events. [10, 11] Anemia is detected in most of the cases at the time of diagnosis in PMF. Besides leukocytosis, leukopenia, thrombocytosis and thrombocytopenia could also be seen. Thrombotic or bleeding complications are common particularly in the presence of thrombocytosis. While focusing on the question of whether there is another condition that predisposing to the generation of thrombosis in CMPD; atherogenic index of plasma (AIP), which is a parameter that causes an increase in the incidence of clot formation in the normal population, shall be one of the first to be considered from the clinical point of view. [12] In those patients with CMPD, there is no extensive data regarding whether the atherogenic index of plasma causes an extra risk for the genesis of thrombus in addition to the RBC and platelet elevation and/or dysfunction. The aim of this study is to assess the atherogenic index of plasma in the patients with CMPD and reveal its relationship between thrombosis, due to the disease course.

METHODS

Study population

Ninety-two patients followed in our clinic with the diagnosis of CMPD and positive for JAK2 V617F gene mutation with real time polymerase chain reaction test and 73 controls randomly selected from patients who applied to the outpatient clinic and had no mutation for CMPD and no CMPD diagnosis pathologically were included in this retrospective cohort study. The sample width was determined by power analysis. The diagnosis of CMPD was made according to the 2016 revision to the World Health Organization classification. 42 of the patients in study group were diagnosed as PV, 30 of them as PMF and the remaining 20 patients as ET. Laboratory data, demographic properties and comorbidities of all participants were retrospectively scanned and noted. Sub-diagnostic groups (ET, PV and PMF) of the patients in the CMPD group and laboratory results used in the diagnosis were recorded. The history of arterial / venous thrombosis was investigated in detail for both groups. Acute myocardial infarction, thromboembolic stroke, deep vein thrombosis, pulmonary embolism, splenic or portal vein thrombosis, acute arterial occlusion defined by imaging methods such as doppler ultrasonography, coronary arteriography or magnetic resonance imaging was defined as the presence of thromboembolic event. The treatments for the primary disease of the patients in the study group were obtained from the from hospital information recorded at patients' regular check-ups. Hypertension (HT) was defined as a systolic blood pressure of 140 mmHg, a diastolic blood pressure of 90 mmHg or more, or a person using antihypertensive medication as mentioned in American Heart Association guidelines. Diabetes mellitus (DM) was defined by according to the American Diabetes Association's 2022 revision criteria as fasting blood glucose is 126 mg/dl and above in at least two tests performed on different days, or if > 200 mg/dL is detected in at least two random blood glucose measurements or if HbA1c values are 6.5% or higher. Smoking habit, a major trigger of thrombosis in CMPD could not be accessible for the patients and control group because of the retrospective design of the study.

Laboratory parameters and calculation of atherogenic index of plasma

Blood samples were collected, and the laboratory measurements of serum values of hematocrit (Hct), hemoglobin (Hb), mean platelet volume (MPV), platelets, red blood cell count (RBC), white blood cell count (WBC), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), red blood cell distribution width (RDW), lipid parameters, kidney function tests were performed and analysed with appropriate kits and atherogenic index of plasma was calculated by using the formula log (Tg/HDL) from serum triglyceride and HDL values. [13] Lipid values were directly measured.

Ethical approval

The study was approved by the local Clinical Research Ethics Committee of our hospital (2022/05-42, 16969557/543). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's hu-

man research committee.

Statistical analyses

All analyses were performed on SPSS 17.0 (SPSS for Windows 20.0, Chicago, IL, USA) and MedCalc for Windows. Data were expressed as mean ± SD for continuous variables and as number and percentage for categorical variables. Normality of the distribution of continuous variables was assessed using Kolmogorov-Smirnov test. The comparisons of the continuous variables between groups were performed using the independent samples t-test and categorical variables with Chi-square test. Univariate and multivariate logistic regression analysis were used to determine the relation between thrombosis and other variables and variables with a p value < 0.25 in univariate analysis were analyzed in multivariate regression. Receiver operating characteristics (ROC) curve analysis was performed to demonstrate the cut-off values and sensitivity and specificity of atherogenic index of plasma for predicting the thrombosis in CMPD. *p* value < 0.05 for all comparisons was considered as significant.

RESULTS

The study group consisted of 30 MF, 42 PV and 20 ET patients. It was estimated that the study would end

Table 1. Baseline demographic properties and laboratory results of the groups

	CMPD group (n = 92)	Control group (n = 73)	*P*
Age, years	63.3 ± 15.2	60.8 ± 13.3	0.281
Sex, male, n (%)	41	25	0.179
HT, n (%)	27	13	0.086
DM, n (%)	9	9	0.772
HF, n (%)	7	3	0.271
COPD, n (%)	2	1	0.637
CKD, n (%)	9	5	0.384
Malignancy, n (%)	8	3	0.278
Hb (g/dL)	12.6 ± 2.5	12.0 ± 2.3	0.147
HTC (%)	39.0 ± 7.8	35.9 ± 6.7	0.008
WBC (10^3/ µL)	8.8 ± 4.3	7.6 ± 5.3	0.125
RBC (10^6/ µL)	4.6 ± 1.1	4.1 ± 0.8	0.002*
MCH (pg)	28.4 ± 4.9	29.3 ± 3.7	0.207
MCV (fL)	87.6 ± 13.0	88.0 ± 9.4	0.831
RDW (%)	19.4 ± 6.1	15.0 ± 2.7	< 0.001*
MPV (fL)	8.7 ± 0.9	8.7 ± 1.2	0.845
PLT (10^3/ µL)	337.5 ± 213.8	247.8 ± 132.4	0.002*
Glucose (mg/dL)	80.2 ± 15.7	72.2 ± 18.2	0.194
Creatinine (mg/dL)	1.0 ± 0.7	0.8 ± 0.3	0.075
Albumin (g/dL)	4.1 ± 0.5	4.2 ± 0.4	0.437
Total protein (g/dL)	7.1 ± 0.6	7.2 ± 0.6	0.808
Total cholesterol (mg/dL)	160.6 ± 50.7	165.4 ± 35.8	0.505
Triglyceride(mg/dL)	134.2 ± 61.6	153.4 ± 65.9	0.060
HDL (mg/dL)	42.0 ± 15.9	49.4 ± 12.6	0.002*
LDL (mg/dL)	102.2 ± 36.4	109.4 ± 31.2	0.186
Tg/glucose index	3.8 ± 2.8	3.3 ± 2.9	0.250
AIP	0.14 ± 0.26	0.01 ± 0.26	0.003*

Abbreviations: CMPD: chronic myeloproliferative diseases, HT: hypertension, DM: diabetes mellitus, HF: heart failure, COPD: chronic obstructive pulmonary disease, CKD: chronic kidney disease, Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell count, RBC: red blood cell count, MCH: mean corpuscular hemoglobin, MCV: mean corpuscular volume, RDW: red blood cell distribution width, MPV: mean platelet volume PLT: platelet count, HDL: high density lipoprotein, LDL: low density lipoprotein, Tg: trigliseride, AIP: atherogenic index of plasma.

Table 2. Univariate and multivariate logistic regression analysis of the studied parameters

	Univariate analysis			Multivariate analysis		
	OR	CI 95%	P	OR	CI 95%	*P*
Age	1.004	0.971-1.037	0.818	-		
Sex	1.450	0.598-3.514	0.411	-		
RBC	1.384	0.912-2.100	0.127	1.152	0.739-1.795	0.043*
WBC	1.060	0.981-1.145	0.340	-		
Hb	1.044	0.869-1.254	0.648	-		
HTC	1.023	0.963-1.087	0.462	-		
MCV	0.992	0.955-1.031	0.697	-		
MCH	0.957	0.866-1.058	0.392	-		
RDW	1.015	0.940-1.097	0.699	-		
MPV	1.244	0.825-1.876	0.298	-		
PLT	1.004	1.002-1.006	0.001	1.003	1.001-1.006	0.003*
Glucose	0.999	0.987-1.011	0.858	-		
Total protein	0.776	0.398-1.515	0.458	-		
Albumin	0.680	0.277-1.667	0.399	-		
Total cholesterol	0.998	0.989-1.008	0.765	-		
Triglyceride	1.004	0.998-1.011	0.267	-		
HDL	0.976	0.946-1.008	0.338	-		
LDL	0.994	0.981-1.007	0.384	-		
AIP	16.291	1.632-16.260	< 0.001	12.580	11.609-13.630	< 0.001*
Tg/HDL	1.104	0.974-1.251	0.121	1.066	0.936-1.213	0.338

Abbreviations: Hb: hemoglobin, Hct: hematocrit, WBC: white blood cell count, RBC: red blood cell count, MCH: mean corpuscular hemoglobin, MCV: mean corpuscular volume, RDW: red blood cell distribution width, MPV: mean platelet volume PLT: platelet count, HDL: high density lipoprotein, LDL: low density lipoprotein, AIP: atherogenic index of plasma, Tg: trigliseride.

with 95% reliability and 80% power, with a minimum of 63 patients for each group. The mean age of the patients in this group was 63.3 ± 15.2 and 60.8 ± 13.3 in the controls ($p = 0.281$). The groups were not different in terms of sex, HT, DM, chronic obstructive pulmonary disease (COPD), chronic kidney disease (CKD), heart failure (HF) and malignancy ($p > 0.005$, for all) but the patients with CMPD had a higher percentage of arterial or venous thrombosis (20% vs 6%) than the controls ($p = 0.019$). Nineteen patients (4 MF, 2 ET and 12 PV) in the CMPD group and 5 patients in the control group had a history of arterial or venous thrombosis. 4 patients in PV and 1 patient in ET had arterial thrombosis (mesentery infarct in two patients, acute ischemic stroke in two patients and myocardial infarction in one patient) and the remaining had venous thrombosis (portal or splenic infarct except one, who had deep vein thrombosis). Four of the patients in the controls had arterial thrombosis (2 myocardial infarction, 2 acute ischemic stroke) and one had deep vein thrombosis in their history. When the groups were compared in terms of laboratory results; we found out that the patients in CMPD group had lower levels of high-density lipoprotein cholesterol (HDL). Although triglyceride to HDL (Tg/HDL) ratio was similar between groups, atherogenic index of plasma was higher in CMPD group and the difference was statistically significant ($p = 0.250$, $p = 0.003$; respectively). Baseline demographic properties and laboratory results of the groups are depicted in Table 1.

Univariate and multivariate logistic regression analysis revealed that platelet count, RBC and AIP were independent predictors for thrombosis in both groups (Table 2). A moderate correlation was found between RBC, AIP, platelet count and thrombosis in correlation analysis ($r = 0.290$, $p < 0.001$; $r = 0.387$, $p < 0.001$ and $r = 0.282$, $p < 0.001$, respectively) and the correlation coefficient of AIP in CMPD group was higher than in the total patients ($r = 0.478$, $p < 0.001$). In ROC curve analysis the platelet count >

Table 3. The comparison of ROC curve analysis of AIP, RBC and platelet count for predicting the risk of thrombosis

	Difference between AUC	SE	CI 95%	Z statistic	P
RBC-PLT	0.0530	0.0948	-0.133-0.239	0.559	0.5759
AIP-RBC	0.2550	0.0921	0.0749-0.436	2.773	0.0056
AIP-PLT	0.2020	0.0750	0.0555-0.349	2.700	0.0069

Abbreviations: SE: standard error, CI: confidence interval, AIP: atherogenic index of plasma, RBC: red blood cell count, PLT: platelet count

270 x 10^3/ µL (sensitivity 78.3%, specificity 45.1%, AUC:0.577), AIP > 0.2 (sensitivity 100%, specificity 43.2%, AUC:0.779) and RBC > 3.34 x 10^6/ µL (sensitivity 39.1%, specificity 77.5%, AUC:0.519) predicted arterial or venous thrombosis risk in study population. Furthermore, the specificity of AIP to predict the risk of thrombosis was better in CMPD group (AUC:0.779, sensitivity 72.2%, specificity 70 %). Comparison of ROC curve analysis showed that AIP was superior to platelet count and RBC in predicting the risk of thrombosis (Table 3, Fig. 1).

DISCUSSION

Vascular complications, especially thrombotic events have commonly seen (nearly one third) in the patients with CMPD who had the JAK2 V617F mutation. [14, 15] Patients with JAK2 V617F mutation had enhanced procoagulation activity and the mutation also itself promotes megakaryocytopoiesis. [7, 16] Two-thirds of thrombosis are arterial in origin. [17] In a previous study by the Italian Polycythemia Working Group 40% of PV patients had arterial or venous thrombosis. Thrombosis has been detected in 12 (28%) of 42 patients with PV in our study, thus the thrombotic rate was lower when compared to the Italian study. In our cohort, microvascular thrombosis is more common and the incidence of transient ischemic attack and unusually located venous thrombosis have increased in the patients with ET. We were able to detect clinical thrombosis within 10% of the patients with diagnosed as ET.

JAK2 V617F positivity is observed in 6,7% patients with Budd-Chiari syndrome and 41% of these patients had the diagnosis of CMPD at the time of thrombosis occurrence or in a year. [18] Trembley and co-workers disclosed that unusual site thrombosis especially in the portal and hepatic veins occurred concurrently (26%) or just after (44%) the diagnosis of

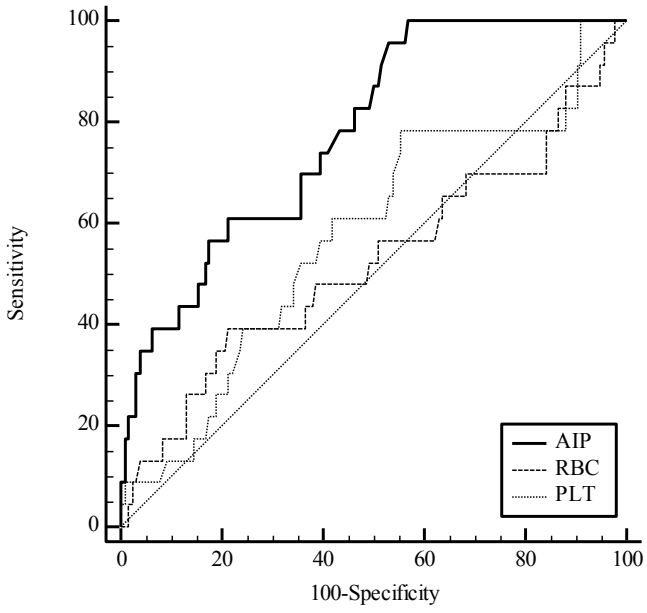

Fig. 1. The comparison of ROC curve analysis
Abbreviations: AIP: atherogenic index of plasma, RBC: red blood cell count, PLT: platelet count

CMPD. [19] Splanchnic vein thromboses were detected 8.1% of the CMPD patients. [20]

Among numerous causes of CMPD thrombosis, the most important factors are the alterations of the elevated number and destructed structure of erythrocytes and platelets. JAK2 V617F mutation carrying newly formed hyperactive thrombocytes can cause platelet aggregation due to the increased turnover. [21] Moreover, over 60 years of age, smoking, the presence of JAK2 V617F mutation especially for ET and any history of thrombosis are considered the most important clinical risk factors for thromboembolic events in various publication and prognostic thrombosis risk scoring models such as International Prognostic Score for Thrombosis in ET (IPSET) and revised IPSET. [22-31] Additional risk factors for thrombosis include cardiovascular risk factors like hypertension, diabetes mellitus and male sex. [32, 33] The results of our study are comparable with those classical concepts of CMPD. Beyond those classical risk factors, there is no study on the existence of different factors that may play a role in clot formation. Kubong *et al*. found that high AIP levels were associated with an increase in oxidative stress in patients with sickle cell anemia, which is also a hematological disease and has a genetic background. [34] Sherief and colleagues determined higher AIP levels in children with beta-thalassemia major and claimed that premature atherosclerosis is related with AIP in those children. [35] There is no other detailed study on this critical biomarker in the hematological diseases. AIP allows us to have information about the viscosity of the blood and is calculated using lipid parameters. AIP has a significant value in terms of both the risk of coronary artery disease and the prognosis of the disease. Likewise, high AIP values were predictive of adverse outcomes in acute ischemic stroke. [36]

There are some limitations of this present study; it is a single centre study with relatively small number of patients and retrospectively designed. Patient dependent factors like smoking or physical activity could not be recorded due to the retrospective nature of the study. This study is including only CMPD patients with JAK2 V617F mutation and the results and the relationship between AIP and thrombosis cannot be generalized for other hematological malignancies and also for other mutations as calreticulin or MPL which are also seen in CMPD. We cannot access the JAK2 V617F allelic burden information of the patients and in this respect, we cannot make comparisons between the groups.

CONCLUSION

In this study, AIP is found to be related with thromboembolism in CMPD patients. Therefore, not only complete blood counts but also other biochemical laboratory values should be closely followed in the CMPD patients. Thrombogenicity biomarkers such as AIP should be taken into account in terms of complications and lipid values follow up should be optimized for the overall management plan of CMPD. Our study with these results contributes to the literature as it provides a little important information on the AIP and CMPD. This small population, single-center study highlights the need for prospective multicenter studies involving other mutations and allelic burden in a large patient population to identify patients with high thrombotic risk.

Authors' Contribution

Study Conception: MK, ÖÖA, ÜYM, İH; Study Design: MK, ÖÖA, ÜYM, İH; Supervision: MK, ÖÖA, İH; Materials: MK, ÖÖA, ÜYM; Data Collection and/or Processing: MK, ÖÖA; Statistical Analysis and/or Data Interpretation: MK, ÖÖA, İH,; Literature Review: MK, ÖÖA; Manuscript Preparation: MK, ÖÖA, ÜYM, İH and Critical Review: MK, ÖÖA, ÜYM, İH.

Conflict of interest

In this article, all authors have stated that there is no conflict of interest between them.

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Is there any relationship between triglyceride and hemogram indices in insulin resistance?

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ABSTRACT

Objectives: We aimed to evaluate the correlation of triglyceride (TG) level with hemogram and biochemical parameters in non-diabetic but insulin resistant and non-insulin resistant obese patients.

Methods: Patients with diabetes, neurological, cardiac and rheumatological diseases were not included in the study. Statistical analysis was performed by recording the hemogram and all biochemical parameters of the patients. The patients were divided into 2 groups. Patients with a HOMA-IR level below 2.7 in group 1 and patients with a HOMA-IR level above 2.7 in group 2.

Results: 70 patients were selected for our study. 24 of these were assigned as those without insulin resistance and were named Group 1 and 46 of these patients were assigned as those with insulin resistance were named Group 2. TG level was found to be lower in Group 1(80.05 + 32.17) compared to Group 2 (176.67 + 16.21) (p = 0.0001).

There was no significant correlation between TG level and hemogram parameters in group 1. In Group 2, TG level and hematocrit (r = 0.475; p = 0.001) showed a significant positive correlation, while platelet lymphocyte ratio (r = 0.474; p = 0.001) showed a significant negative correlation. In Group 2, TG and ferritin (r = 0.421; p = 0.004) showed a significant positive correlation.

Conclusion: In obese patients without diabetes, triglyceride levels were found to be high in those with high insulin resistance. The significant correlation of triglyceride level with hct, PLR and ferritin in insulin resistance reveals the importance of these parameters in the atherosclerotic process.

Keywords: Insulin Resistance, Triglycerides, Hematocrit, Lymphocytes, Blood Platelets, Ferritin

Insulin resistance is an important and reversible risk factor for diabetes. [1] Hypertriglyceridemia (HTG) has an important place in metabolic disorders. Lifestyle factors and genetic play important role in the pathophysiology of hypertriglyceridemia. HTG, in cases of accompanying insulin resistance, is an indispensable fact that cardiovascular diseases (CVD) are also increasing. [2] HTG is also a risk for the formation of pancreatitis. [3] In this study, we performed evaluated the relationship between biochemical parameters and hemogram with TG levels, especially in patients with and without insulin resistance.

METHODS

Patients aged 18-75 years were included in this study. Patients with cardiac, rheumatological, neu-

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rological, diseases, diabetes, and malignancies were not included. Hemogram and all biochemical parameters of the patients were recorded as laboratory findings studied in a single center when they applied to the internal medicine clinic. Patients divided into two groups: Group 1 patients with HOMA-IR level below 2.7; Group 2 Patients HOMA-IR level above 2,7. In these groups, triglyceride levels was compared with hemogram parameters such as hb (hemoglobin), Hct (hematocrit), MCV (mean erythrocyte volume), platelet, MPV (mean platelet volume), PDW (platelet distribution width), WBC (leukocyte), lymphocyte, neutrophil, PLR (platelet/lymphocyte ratio). NLR (neutrophil/lymphocyte ratio) Triglyceride levels were also compared with other biochemical parameters such as age, BMI (body mass index), ALT (alanine aminotransferase), AST (aspartate aminotransferase), GGT (gammaglutamyl transferase), FBC (fasting blood sugar), HOMA-IR (Insulin resistance), Insulin, HbA1C was BUN (blood urea nitrogen), Creatinine, HDL (high-density lipoprotein), LDL (low-density lipoprotein), ferritin, TSH (Thyroid-stimulating hormone) and CRP (C-reactive Protein).

T test was used for statistical comparison. SPSS for Windows V.24.0 (SPSS Inc. Chicago, IL) package program was used for statistical evaluations. Obtained values were given as mean ± standard deviation or as numbers and percentages. The level of significance in the evaluations was accepted as $p < 0.05$. Whether the data met the parametric conditions for the measurement variables of the two groups was evaluated using the Kolmogorov Smirnov Test.

The values of the measurement variables were compared between groups using the Student's t-test, those that did not fit the normal distribution, and the Mann-Whitney-U test. Spearman was used in correlation analysis and kruskal valis was used in comparison of 2 different groups.

RESULTS

70 patients were selected for our study. 24 of these were assigned as those without insulin resistance and were named Group 1 and 46 of these patients were assigned as those with insulin resistance were named Group 2. TG level was found to be lower in Group 1(80.05 + 32.17) compared to Group 2 (176.67 + 16.21) ($p = 0.0001$). Group 2 was accepted as HTG. While no significant correlation was found between TG level and hemogram parameters in Group 1, Hb (r = 0.404; $p = 0.005$), Hct (r = 0.475; $p = 0.001$), MCV (r = 0.424; $p = 0.003$), in Group 2, WBC (r = 0.335; $p = 0.023$) showed a significant positive correlation with lymphocyte (r = 0.406; $p = 0.005$), while it showed a significant negative correlation with PLR (r = 0.474; $p = 0.001$) (Table 1).In the correlation analysis between triglyceride and biochemical parameters, TG showed a positive correlation with age (r = 0.429; $p = 0.036$) and TSH (r = 0.441; $p = 0.031$) in Group 1, while ALT (r = -0.473; $p = 0.020$) showed a negative correlation with In Group 2, TG and AST (r = 0.350; $p = 0.017$), ALT (r = 0.353; $p = 0.016$), GGT (r = 0.381; $p = 0.009$), BUN (r = 0.365; $p = 0.013$), Positive with creatinine (r = 0.286; $p = 0.054$), Total cholesterol (r = 0.567; $p = 0.0001$), LDL (r = 0.531; $p = 0.0001$) and

Table 1. Correlation of triglyceride level with hemogram parameters

Triglyceride	Group 1 n = 24		Group 2 n = 46	
	R value	*P* value	R value	*P* value
Hemoglobin	-0.017	0.935	0.404**	**0.005**
Hematocrit	-0.216	0.311	0.475**	**0.001**
MCV	0.211	0.322	0.424**	**0.003**
Platelet	0.205	0.336	-0.035	0.816
PDW	0.223	0.296	0.007	0.962
MPV	-0.107	0.620	-0.013	0.932
Leucocyte	0.140	0.514	0.335*	**0.023**
Neutrophil	0.038	0.861	0.079	0.602
Lymphocyte	0.084	0.695	0.406**	**0.005**
NLR	-0.073	0.736	-0.233	0.119
PLR	0.071	0.740	-0.474**	**0.001**

MCV: mean corpuscular volume; PDW: platelet distribution width; MPV: mean platelet volume; NLR: neutrophils/lymphocyte ratio; PLR: platelet/lymphocyte ratio

Table 2. Correlation of triglyceride level with biochemical parameters

Triglyceride	Group 1 n = 24		Group 2 n = 46	
	R value	*P* value	R value	*P* value
Age	0.429*	**0.036**	0.096	0.524
BMI	-0.137	0.524	0.038	0.800
AST	-0.243	0.253	0.350*	**0.017**
ALT	-0.473*	**0.020**	0.353*	**0.016**
GGT	-0.110	0.608	0.381**	**0.009**
Glucose	0.040	0.854	0.268	0.072
Insulin	0.156	0.467	0.049	0.748
HOMA-IR	0.131	0.542	0.223	0.136
HbA1c	-0.245	0.249	0.223	0.137
BUN	0.045	0.835	0.365*	**0.013**
Creatinine	-0.376	0.070	0.286	**0.054**
Total cholesterol	0.345	0.099	0.567**	**0.000**
LDL	0.221	0.300	0.531**	**0.000**
HDL	-0.251	0.248	-0.496**	**0.000**
TSH	0.441*	**0.031**	0.196	0.192
Ferritin	-0.122	0.571	0.421**	**0.004**
CRP	0.365	0.080	-0.206	0.170

BMI: Body mass index; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; GGT: γ-glutamyl transferase; HOMA-IR: homeostasis model assessment of insulinresistance; HbA1c: Hemoglobin A1c; BUN: blood urea nitrogen; LDL: low density lipoprotein-cholesterol; HDL: high density lipoprotein cholesterol;TSH: thyroid-stimulating hormone ;CRP: C-reactive protein

ferritin (r = 0.421; $p = 0.004$) while it correlated negatively with HDL (r = -0.496; $p = 0.0001$) (Table 2).

DISCUSSION

In this study, we evaluated the relationship between HTG and hemogram indices in patients with insulin resistance. The main link in this relationship may be inflammation and oxidative stress. Blood cell count is a commonly applied detection method. Among the blood cells, white blood cell count (WBC) and erythrocyte blood cell (RBC) count are associated with insulin resistance and metabolic syndrome. [4-6] In this study, we also found that HTG in patients with insulin resistance; we found that it showed positive correlation with WBC, lymphocyte, Hb and Hct. We did not find a relationship between TG and hemogram parameters in our control group patients without insulin resistance. Hct is the most important determining factor for blood flow velocity. If Hct is elevated, blood viscosity increases markedly, which also reduces blood flow velocity and glucose delivery from the blood to the muscles. This leads to insulin resistance. [7] In fact, some studies have found that phlebotomy significantly improves insulin resistance and diabetes. [8, 9] When hypertriglyceridemia is added to it, blood viscosity increases even more. [10]

Total white blood cell, subtypes and their ratios (Neutrophil, Platelet, Eosinophil-Lymphocyte ratio; NLR, PLR, ELR ratio) in other blood parameters have been used as an indicator of chronic inflammation recently. [11-16] PLR is an inflammatory parameter that has been defined in recent years and can be easily calculated from a complete blood count. It has been reported that severity of inflammation is associated with the high PLR. [17] In our study, we found that HTG showed a negative correlation with the PLR. PLR is an indicator that shows changes in lymphocyte and platelet counts due to prothrombotic and acute inflammatory conditions. PLR has been studied, especially in neoplastic diseases accompanied by thrombosis and immunosuppression. In the literature, it has been suggested that PLR has prognostic importance in cardiovascular diseases and diabetes mellitus, hypertension, hepatic cirrhosis, familial Mediterranean fever and malignancies. [18] Many large-scale studies have used the variation in PRL to predict the severity of inflammation in rheumatic diseases. [19]

Ferritin concentration, another parameter of ours, is

associated with metabolic syndrome [20, 21] and non-alcoholic hepatosteatosis; [22] and these abnormalities can also lead to carotid atherosclerosis. [23] In our study, it was found that TG levels were positively correlated with ferritin in patients with insulin resistance. In a study, it was found that insulin resistance and liver enzyme levels improved when iron was removed by phlebotomy in patients with familial hypertriglyceridemia. [24] Looking at other parameters, high serum LDL cholesterol level is an important risk factor for cardiovascular disease (CVD), especially for coronary artery disease.

Lowering LDL cholesterol levels lowers the risks of CVD and reduces its mortality and morbidity. [25-26] However, the role of high triglyceride levels in CVD is still controversial. The atherogenic effect of triglycerides has long been unclear. Controversy over hypertriglyceridemia as an independent risk factor for CVD has arisen in part because high triglyceride levels are often a component of atherogenic dyslipidemia, which are associated with increased levels of LDL cholesterol and lower HDL cholesterol levels. Today, however, results from large studies show that high levels of fasted or fed triglycerides, particularly triglyceride-rich lipoproteins, and their residues, are independently associated with an increased risk of CVD. [27, 28] In our study, we found that high TG levels were associated with hypercholesterolemia and negatively correlated with HDL cholesterol levels. The presence of hypercholesterolemia and hypertriglyceridemia in insulin resistant patients are serious risk factors for CVD.

HTG is also associated with non-alcoholic fatty liver disease, and studies have shown that it is more associated with fatty liver, especially when compared to other LDL and HDL cholesterol. [29, 30] We compared triglyceride and liver enzymes, and we found a positive correlation in our study.

CONCLUSION

As a result, TG levels were found to be associated with both hemogram parameters (Hb, Hct, lymphocyte, PRL) and other biochemical parameters (such as cholesterol levels, liver enzymes and ferritin) in patients with insulin resistance when compared with the control group. In some previous studies, it was thought that these values may be related to each other, especially since they are components of the metabolic syndrome. So, to reduce both insulin resistance and TG levels, first of all, dieting, especially reducing carbohydrate intake; doing regular exercise, using drugs that reduce TG levels and reduce insulin resistance will be a precaution for future CVD.

In obese patients without diabetes, triglyceride levels were found to be high in those with high insulin resistance. The significant correlation of triglyceride level with hct, PLR and ferritin in insulin resistance reveals the importance of these parameters in the atherosclerotic process.

Authorship Contributions

Concept: S.C., O.O, Data Collection or Processing: S.C., Analysis or Interpretation: O.O., Literature Search: S.C., Writing: S.C., O.O.

Financial Disclosure

The authors declared that this study received no financial support.

Conflict of Interest

No conflict of interest was declared by the authors.

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Evaluation of Polypharmacy in Individuals over 65 Years of Age in Balçova District of Izmir

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ABSTRACT

Objectives: The morbidities and long-term multiple medication use among elderly.

Methods: The study was conducted by the 2nd grade medical students from Izmir University of Economics under the supervision of instructors. In this descriptive cohort, the study sample included 45 individuals over 65 years of age among the identified 150 residents in Balcova. The response rate was 26.4% for men and 73.3% for women. A questionnaire was defined for a face-to-face interview, which included sociodemographic variables, medical history, lifestyle, systems inquiry, and a detailed list of all medications.

Results: Mean age of the elderly was 78.5 ± 7.2 years. Women, widows, and primary school graduates constituted the majority. Hypertension, osteoarthritis, and osteoporosis were the leading morbidities by 71.1, 46.7 and 31.1% respectively. Stroke, kidney disease and migraine were the least morbidities by 3%. 66.7% were using five or more than five medications, 93.3% were using medications prescribed by the doctor, none complained of adverse effects, 4.4% were non-compliant to treatment and 28.9% were using vitamin supplements and herbal remedies.

Conclusion: Increase in the prevalence of age-related chronic diseases is accompanied by an increase in polypharmacy,

Key words: Polypharmacy, elderly, community-based health practice

Prescriptions are the second most expensive component of health-care expenditures in developed countries. [1-3] The use of pharmaceuticals to treat chronic diseases and ailments (such as heart disease, high cholesterol, hypertension, diabetes, and depression) is becoming more common. [4-5]

According to World Health Organization (WHO) data, the global population of elderly is increasing every year due to increased life expectancy. While there were 580 million people over the age of 65 in 1998, this number is anticipated to rise to 1.97 billion by 2050. [6] As people live longer, managing many chronic diseases becomes more critical. [7] Prescription medications are used to treat both physical and mental ailments. 8 As life expectancy increases, so do health issues, particularly cardiovascular diseases and musculoskeletal disorders. [9, 8]

Multiple drug usage (polypharmacy) is defined as the use of more than one drug at the same time and is a common concern in old age. Although there are many pharmaco-epidemiological studies on this topic in developed countries, there are quite few in our country.

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[7] Antibiotics, antihypertensives, and analgesics are among the pharmacological categories that have been linked to adverse effects when combined with other medications. [11, 12]

The American Geriatrics Society (AGS) maintains a list of unsuitable drugs for people 65 and older based on the regularly updated AGS Beers Criteria®, which is related to safe drug use in the elderly. Since the last update, a professional panel of 13 members has systematically evaluated the evidence and released the update in January 2019. Thirty potentially unsuitable drugs/drug classes are included in the new AGS Beers Criteria for older adults. In addition, there are 40 conditions that should be avoided or used with caution in the elderly. [13, 14] The Beers Criteria®, a management tool. [13, 14] have now been removed because researchers have demonstrated that it causes a rise in the costs. [13, 14]

The aim of this study was to evaluate the prescription and /or usage of medicines among elderly people via face-to-face interview technique during home visits. This study was developed specifically for the senior population, where long-term and multiple drug use is frequent, in order to understand the causes of multiple drug use and to offer sensible drug use advice.

METHODS

In the 2018-19 academic year, medical students (36 second-year students) and nurses (31 third-year students) coordinated the community-based health practice (CBHP), which also included elderly care and physiotherapy (44 first-and second-year students). The students from the nursing-medical and physiotherapy-elder care programs were paired up. Students attended lectures on the biopsychosocial characteristics of the elderly, geriatric risk factors, and communication techniques before the house visits. The neighborhood was identified as the university district, Balçova, within the parameters of the project. With the assistance of the district municipality, about 120 elderly people were shortlisted. Elderly people who had been previously informed about the project were visited at home by faculty members who shared information with them. The final group included 45 elderly people who gave permission for the house visits. The faculty members set up the appointments. Over the course of a six-week period, each student group paid the designated elderly person three visits.

In this study, it was aimed to evaluate multiple medication usage among a community sample over age 65 who are living in their own home in the vicinity of Izmir University of Economics of Balçova district in İzmir. The research was planned in a descriptive-cohort design. All of those who gave consent to the study were included in the research group by face-to-face interview. The records of the health information of the elderly, their sociodemographic characteristics and the questionnaire prepared by the researchers were applied through face-to-face interviews.

The statistical analysis was performed by SPSS (statistical package for social sciences, SPSS Inc., Chicago) package program. Descriptive analysis, the mean and standard deviation was used for continuous variables, the median and interquartile range was used in the absence of a normal distribution in variables, and number and percentage was used for categorical variables.

RESULTS

Mean age of the elderly was 78.5 ± 7.2 years. Women, widows, and primary school education constituted the majority.

Hypertension, osteoarthritis, and osteoporosis were the leading morbidities by 71.1, 46.7 and 31.1% respectively. Stroke, kidney disease and migraine were the least morbidities by 3%. Among elderly population, 28.9% had six or more than six morbidities, 66.7% were using five or more than five medications, 6.7% were without medication, 93.3% were using medication prescribed by the doctor, none complained of adverse effects, 4.4% were noncompliant to treatment and 28.9% were using vitamin supplements and herbal remedies.

This study was a cross-sectional study. Unfortunately target population couldn't be reached. Although the insufficient number of samples, we wanted to present its results and discuss its contribution to the literature.

DISCUSSION

In our study, 28.9% had six or more than six morbidities, 66.7% were using five or more than five medications. According to BEERS criteria, defining polypharmacy through daily drug usage is insufficient. Drug-drug interactions are crucial, too. For example,

"Ciprofloxacin in combination with theophylline increases risk of theophylline toxicity. The concurrent use of a combination of three or more central nervous system (CNS) agents (antidepressants, antipsychotics, benzodiazepines, nonbenzodiazepine benzodiazepine receptor agonist hypnotics, antiepileptics, and opioids) and increased fall risk have been collapsed into one recommendation instead of separate recommendations for each drug class". [13] So these participants were at risk of their chronic conditions and also drug-drug interactions.

Olgun *et. al.* has revealed that *"...following medicines had inappropriate prescribing according to AGS Beers Criteria®: nifedipine (n = 410) 68.8%, amiodarone (n = 43) 44.2%, CNS medicine (n = 506) 21.5%, barbiturate (n = 67) 0%, glimepiride (n = 177) 53.7%, and PPI (n = 2052) 29.2%. While the prevalence of inappropriateness, as determined by Beers Criteria® and similar criteria, ranges from 13 to 35% worldwide, it is 23% in European countries and 33% in our country."* [14] In this study the electronic records of 66136 prescriptions belonging to 13906 different patients and processed in a pharmacy in Istanbul between January 2014 and February 2019 were analyzed. [14] Although our sample is less and the data collection was performed according to the self-information, polypharmacy rate was similar.

Silva et al revealed that "Herbal supplements are popular among the elderly, a society that takes a larger amount of prescription medications when compared to younger populations. Among the issues raised by these studies was a lack of communication between patients and healthcare providers regarding the use of herbal supplements. When making pharmacological treatment decisions, prescribers must consider the use of herbal supplements and consult with their elderly patients." [16] In terms of the most commonly used herbal supplements, gingko biloba and garlic are both known to be beneficial in chronic diseases that are more common in the elderly. Gingko biloba is widely used for its reported effects on memory, concentration, and cognitive dysfunction treatment. However, combining gingko with prescription and over-the-counter medications can result in dangerous drug interactions. The combination of gingko and antiplatelet drugs and/or anticoagulants may increase the risk of bleeding complications because both gingko and these drugs reduce the ability of the blood to clot. [17] In our study 28.9% of the participants were using vitamin supplements and herbal remedies. This was approximately same as the study of Agbabiaka et al. [18] To improve knowledge and skills about polypharmacy, MOOC trainings could be a useful and appropriate tool for the physicians while not only polypharmacy but also chronic conditions are still main problems for elderly. [19, 20, 21]

Medication Use In The Elderly

Physiological effects in the elderly that may alter medication. These changes include drug absorption by tissues, diffusion, use in the body, excretion, and impact, which results in receptor sensitivity in predicted tissues. The elderly are affected differently depending on the changes. [22]

Drugs that depress the central nervous system, antibiotics, analgesics, anticoagulants, and antihypertensives are the most prevalent side effects among the elderly, followed by bronchodilators, diuretics, and oral hypoglycemic medicines. [23, 24]

It's possible that it's a medicine adverse effect. The following findings are required in the elderly: sortable; sadness, confusion, restlessness, falling, memory loss, extrapyramidal system findings (Parkinsonism, tardive dyskinesia), constipation, and incontinence. [25]

There are some dangers associated with increasing compliance with pharmacological therapy and ensuring safe use. It is critical to understand the variables. For example, the elderly individual should be asked what he does when he forgets, whether he knows the side effects of the drugs he uses, which side effects the purpose of use of the recommended drugs and the drug, whether he knows the duration of use, whether he has used these drugs before, and whether he has used aids such as a reminder note, alarm, or medicine box benefit. Similarly, social security status, pharmaceuticals from the budget if he/she can afford them, whether he/she has financial troubles, and ultimately, whether she feels better following drug therapy. [24]

Academic Geriatrics Association, a total of 49 expert (consultant) faculty members from (12 different departments and 5 different Internal Diseases Departments) and 23 working groups participated under the leadership of the Academic Geriatrics Association Rational Medicine Working Group, with the wide participation of faculty members who are experts in their fields and experienced in the clinical practice of elderly patients in Turkey has reported the Turkish Inappropriate Medication Use in the Elderly (TIME) Criteria as "TIME-to STOP and 41 TIME-to START". [26] These tools also could help physicians not to tend to "polypharmacy". Although we couldn't reach the target population, our findings revealed that most of the individuals were not complaining about side-effects.

Follow-up of physicians seems essential for wellness of elderly to prevent them from global risk of "polypharmacy". [27]

CONCLUSION

Increase in the prevalence of age-related chronic diseases is accompanied by an increase in polypharmacy, which carries health risks of noncompliance to treatment. Well-structured patient follow-up for elderly with improved tools could prevent from the negative effects of polypharmacy.

Authors' Contribution

Study Conception: OG, DES, HP, MKY, IS,; Study Design: OG, DES, HP, MKY, IS,; Supervision: OG, IS; Materials: OG, DES, HP; Data Collection and/or Processing: HP, MKY, IS; Statistical Analysis and/or Data Interpretation: OG, DES, IS; Literature Review: OG, DES; Manuscript Preparation: OG, DES, IS and Critical Review: OG, DES, HP, MKY, IS.

Conflict of interest

None to declare

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Case report

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A rare disorder of sex development: de la Chapelle syndrome

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ABSTRACT

Sex reversal syndromes can be summarized as incompatibility of chromosomal sex and gonadal characteristics. A very rare syndrome. 46 XX testicular disorder was first described by De La Chapelle in 1964 in 46 XX karyotype, male individuals. Generally, patients whose phenotype is male apply to the health center with infertility, impotence, loss of libido or gynecomastia. The translocation of the part of the Y chromosome, including the SRY (sex-determining region Y) gene, to the X chromosome during paternal meiosis is responsible for etiopathogenesis.

In our case, a 38-year-old male patient applied to our outpatient clinic with the complaint of enlargement in both breasts. His beard-mustache and body hair distribution were normal, he has bilateral grade 2 gynecomastia, penis length was 7 cm, testicles were small, and palpable in the scrotum. Laboratory values were compatible with hypergonadotropic hypogonadism and in the sperm analysis azoospermia was detected. Karyotype analysis was 46 XX, SRY was also studied with FISH (Fluorescence in Situ Hybridization) technique. The patient was diagnosed with 46 XX Testicular Disorder (de la Chapelle Syndrome) and testosterone replacement therapy was started.

We aimed to present the diagnosis and management of De La Chapelle Syndrome in our case.

Keywords: Disorder of sex development, gynecomastia, 46 xx males

Sex reversal syndrome can be summarized as the incompatibility of chromosomal sex and gonadal characteristics. 46 XX testicular disorder is a very rare syndrome that was first described by De La Chapelle in 1964 in men with a 46 XX karyotype. [1] It is seen in one in 20000 newborns. [2] In the classic type, individuals are usually male phenotype and of normal height. Somatic anomalies are not expected, and intelligence is normal. [3] Although the testicles are located in the scrotum, they are quite small in size. Gynecomastia is common. No fertile cases have been reported, azoospermia and infertility appear in every case. Although very rarely, spermatogonia can be found in the ejaculate. [4] In addition to the classical type, there are also variants with ambiguous genitalia and true hermaphroditism. [5] Generally, the reasons for admission to the hospital are gynecomastia and infertility.

CASE REPORT

A 38-year-old male patient was admitted to the Sultan Abdulhamid Han EAH Endocrinology and Metab-

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olism Diseases Outpatient Clinic with the complaint of enlarged breasts. He stated that the enlargement of the breast had been for many years. He did not have any comorbidities or any medication that he used regularly. He complained of sexual reluctance, erectile dysfunction and absence of ejaculation. Although he has been married for 12 years, he has no children. On physical examination his height was160.9 cm, weight was 75.2 and body mass index was 29. There were grade 2 gynecomastia in both breasts, more prominent on the right. Penis length was 7 cm. Although the testicles were smaller than normal, they could be palpated in the bilateral scrotum. In laboratory tests, TSH: 0.7006 uIU/mL (0.35-4.94), Free T4: 1.05 45 ng/dL (0.7-1.48), Total Testosterone: 1.04 ng/mL (1 .66-8.11), Prolactin: 7.66 ng/mL (3.46- 46 19.40), FSH: 34.13 mIU/mL (0.95-11.95), LH: 12.51 mIU / mL (0.57-12.07), Estradiol (E2): < 10 pg/mL (11.3-43.2).

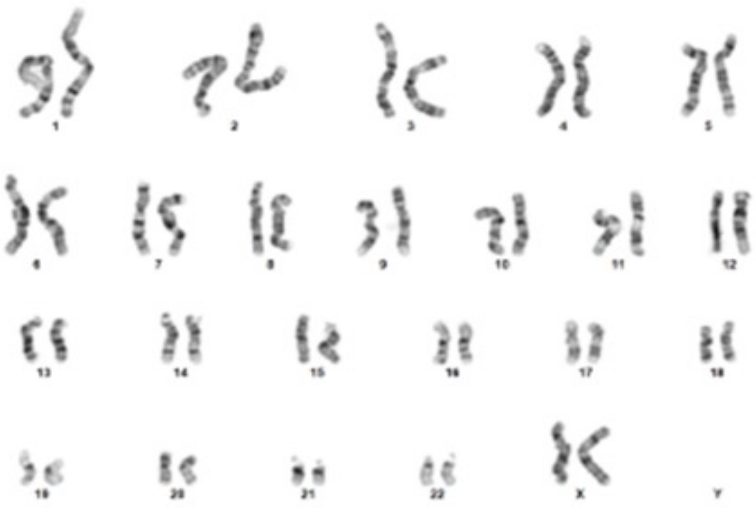
Breast ultrasonography was performed: There is bilateral gynecomastia, more prominent on the right. No mass lesion was observed. His mammography: Bilateral gynecomastia appearance is present. Breast density was more prominent in the right breast. His scrotal ultrasonography: Right testis was 15 x 9 x 15 mm (1.1 cc), left testis was 17 x 10x13 mm (1.3cc), and testis dimensions were reduced.

Karyotype analysis was requested from the patient. The karyotype analysis revealed 46, XX (Fig. 1). Simultaneous microdeletion analysis revealed deletion in AZFa AZFb AZFc regions. SRY was positive in amplification by FISH (fig. 2).

After all these examinations, the patient was started on 100 mg of testosterone decanoate and gradually the dose of 300 mg/month was reached. No side effects were observed that would cause the patient to discontinue treatment. He stated that there was an improvement in sexual functions. The patient was screened for osteoporosis by bone mineral densitometry. No osteoporosis or osteopenia was detected. After explaining the current illness to the patient, he was referred for psychosocial support.

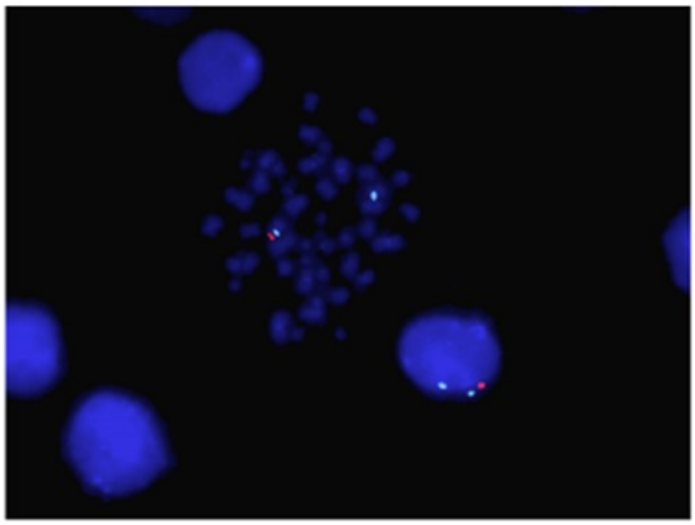
DISCUSSION

The SRY gene localized on the Y chromosome is responsible for the testicular determining factor (TDF), and this factor constitutes the most important step in sex development. [6] In 46 XX male syndromes, 90% of patients have Y chromosomal material, including the SRY gene. It is stated that this material is located at the end of the short arm of the paternal X chromosome by Y-X translocation during meiosis. [7] The presence of the SRY gene is responsible for the formation of the masculine phenotype; Indeed, ambiguous genitalia appears more frequently in 46 XX male syndrome without Y chromosome material and SRY gene. [8] Although this is the most frequently discussed theory, there may be an X-linked somatic mutation responsible for testicular differentiation or a Y mosaicism found only in the gonads. [8] It is thought that the SOX-[9]



Karyotip: 46,XX

Fig. 1. The karyotype analyses of the patient



Karyotip: ish (DXZ1x2, DYZ1x0, SRYx1) [100]

Fig. 2. The FISH analyses show that SRY gene region is located on the chromoseome X. One orange (SRY) and two aqua (DXZ1) signasls were recognised.

gene is affected in X-linked mutations and this gene behaves like SRY. [9] There are AZF (Azoospermia factor) gene families responsible for azoospermia on the Y chromosome. Gene regions subdivided as AZFa, AZFb, AZFc and AZFd encode proteins responsible for sperm maturation. [10] AZF mutations are very common in patients with 46 XX testicular disorders. [11]

In the classical type, which includes 90% of the patients, there are usually no signs before puberty. Insufficient testicular development after puberty, gynecomastia, and adult infertility are the most common reasons for admission to the hospital. The phenotypes of the patients are masculine with adequate terminal hair growth, as in our case. Testicles are usually less than 5 ml, hypospadias or undescended testicles can be seen in a few of them. All are infertile. Breast ultrasonography is compatible with gynecomastia. [5] SRY is negative in 10% of patients and these patients may have ambiguous genitalia. Patients are at risk of osteopenia/osteoporosis and low muscle mass due to hypogonadism. They also suffer from erectile dysfunction. Psychiatric comorbidities are common. [12]

The diagnosis of the disease can be made by clinical, laboratory and cytogenetic studies. Hypergonadotropic hypogonadism predominates in the laboratory. After puberty, testosterone is low and serum FSH and LH are high. 11 In 90% of these patients with 46 XX in cytogenetic analysis, the SRY gene is found to be positive by FISH or PCR. [8] AZF mutations are common.

Testosterone replacement should be given in cases with clinical and laboratory androgen deficiency. Testosterone replacement can be started from puberty. Patients should also be investigated for osteoporosis and closely monitored for testosterone side effects. Surgery may be recommended in cases with external genital anomalies or severe gynecomastia. Every diagnosed patient should be given psychosocial support. [9]

CONCLUSION

We diagnosed the patient who applied to our outpatient clinic with gynecomastia, as a result of laboratory and genetic examinations, with “De La Chapelle Syndrome”. We started testosterone replacement therapy, referred for psychological support and scanned for osteoporosis. Although De La Chapelle Syndrome is a very rare syndrome, it should be kept in mind in men with infertility or gynecomastia and genetic consultation should be requested in appropriate patients.

Authors’ Contribution

Study Conception: MCŞ, İE, NHE, SC, FD, AY; Study Design: MCŞ, İE, NHE, SC, FD, AY; Supervision: MCŞ, İE, NHE, SC, FD, AY; Materials: MCŞ, İE, NHE, SC, FD, AY; Data Collection and/or Processing: MCŞ, İE, NHE, SC, FD, AY; Statistical Analysis and/or Data Interpretation: MCŞ, İE, NHE, SC, FD, AY; Literature Review: MCŞ, İE, NHE, SC, FD, AY; Manuscript Preparation: MCŞ, İE, NHE, SC, FD, AY and Critical Review: MCŞ, İE, NHE, SC, FD, AY.

Conflict of interest

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