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Treatment of overweight and obesity during and after a pandemic. Let's not wait for the development of complications — new guidelines for doctors

Guidelines developed by Experts endorsed by the Polish Association for the Study of Obesity, Polish Psychiatric Association, Polish Society of Hypertension, Scientific Section of Telepsychiatry of the Polish Psychiatric Association, Polish Association of Cardiodiabetology, Polish Association of Endocrinology, and The College of Family Physicians in Poland

Social patronage of the Foundation for People with Obesity OD-WAGA

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Abstract

The treatment of obesity in the pandemic era has become more important than ever. The current situation is conducive to the worsening of disease and the development of new diseases, mainly as a result of compensating negative emotions with food. Taking into account the data on the impact of obesity and its complications on the severity of the course and the risk of death due to COVID-19, we recommend using the 2016 American Endocrine Society's criteria for the diagnosis of obesity instead of the 1998 WHO criteria. We also recommend diagnosing eating under the influence of emotions and the occurrence of eating disturbances, such as compulsive eating syndrome, night eating syndrome and food addiction, and complications of obesity, in any person with a BMI ≥ 25 kg/m^2.

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The approach to treatment should be individualised and should not be limited to nutritional and physical activity education alone. Each patient should be offered appropriately selected pharmacotherapy, and, if necessary, also psychotherapy. The first-line drug should be a combined preparation containing naltrexone and bupropion (Mysimba®). Liraglutide in a dose of 3 mg (Saxenda®) should be considered as a second-line drug in a situation where eating under the influence of emotions is excluded (reaching for food in situations of experiencing negative and positive emotions and boredom, eating disturbances: compulsive eating syndrome, night eating syndrome, and food addiction) and depressed mood or there are permanent contraindications to the use of the first-line drug.
It is unethical not to treat obesity or refer the patient to another doctor for treatment. The use of telemedicine tools can facilitate work in therapeutic teams (doctor, dietitian, psychotherapist), as well as improve patient compliance with pharmacotherapy and changes in eating habits and the level of physical activity recommendations.

Key words: obesity treatment; pharmacotherapy; telemedicine; guidelines for doctors

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Preamble

Obesity has been recognised as a disease by the World Health Organisation (WHO) for many years and is included in the International Classification of Diseases (ICD-10) under number E.66.

The WHO defines obesity as abnormal or excessive accumulation of fat in adipose tissue causing deterioration of health. The health consequences of obesity depend on the degree of excess body fat, its distribution, and the duration of obesity. It is a chronic disease without a tendency to spontaneously resolve, but with a tendency to relapse. It is not a metabolic disease. It should be noted that, it is a disease of a complex aetiology in which various causative factors lead to eating disturbances that cannot be counteracted by physical activity, resulting in a positive energy balance and the storage of excess energy in adipose tissue. Increasingly, obesity is classified as a psychosomatic disease.

Overweight is a condition defined as pre-obesity, in which the degree of excess fat that does not yet meet the criteria for diagnosing obesity [1].

Contrary to popular belief, obesity is not the fault of the patient. Blaming the patient for being ill is not ethical and leads to a lack of effective treatment, and as a consequence the disease progresses, its complications develop, the quality of life deteriorates, disability develops, and life expectancy shortens [2].

The contemporary approach to making therapeutic decisions is based on the principles of biomedical ethics published in the late 1970s, including patient autonomy, benefits and safety, and fairness.

How the autonomy of a patient with obesity is violated:

- Lack of access to an appropriate obesity treatment system and reimbursement of drugs supporting its treatment, as well as specialist medical advice, dietary advice, and psychotherapy.
- The archaic and pejorative view that obesity is the result of a lack of discipline and self-control, also among healthcare workers. This stigmatises obese patients, influences their patient judgment, interpersonal behaviour, and treatment decisions.
- Patients' negative experiences from previous contacts with healthcare professionals lead to stress and avoidance of seeking care, distrust of doctors, and non-compliance with their recommendations.

It should be emphasised that stigma and prejudices restricting access to appropriate treatment are an unacceptable violation of the patient's right to autonomy.

Ethical benefit and security are based on the principle "Do No Harm First". In this context, there are two dimensions: individual and social. In the individual dimension, the ethical aspect includes not recommending methods of diagnosing and treating obesity, the effectiveness and safety of which have been scientifically proven, and not informing the patient about all methods that can and should be applied to him/her. However, in social terms, there is a tendency to blame obese patients for the fact that their excess body mass results in a cost to other members of society. Interestingly, patients with complications of obesity are not blamed for the fact that they suffer from them, which creates a paradox, e.g. you are guilty that you suffer from obesity, but it is not your fault that you suffer from one of its most common complications: type 2 diabetes. It is unethical to blame obese patients for exposing other members of society to costs because they are not provided with appropriate medical care in accordance with current knowledge.

Justice in terms of etical includes resource constraint, respect for individual rights, and adherence to established laws.

Patients diagnosed with obesity experience inequalities in health and limitations in self-determination not only because of the underlying disease, but also when they develop other chronic diseases due to the lack of equipment and negative attitudes of medical staff caused by stereotypical thinking, and lack of knowledge in the field of obesity treatment and inability to refer the patient to an obesity treatment centre [2, 3].

The principles of an ethical approach to obesity, developed by the American Society of Gynaecologists and Obstetricians, show that negative attitudes towards obese patients occur even among doctors specialising in obesity treatment. The conducted studies show that the reasons for this negative attitude are very different from the fact that the doctor also suffers from obesity to the aforementioned blaming patients for their disease, perceiving them as problematic and time-wasting. It has been observed that this results in a disturbance of the doctor–patient relationship because doctors show less empathy towards obese patients, are less likely to engage in counselling and patient-centred care, and paradoxically spend less time on them. Such an attitude of a doctor may delay the proper diagnosis of the cause of obesity and initiate effective treatment. Moreover, a patient who has experienced prejudice or stigmatisation may avoid treatment not only of obesity, but also of its complications. It has been shown, inter alia, that neoplasms in obese patients are diagnosed at a high degree of advancement because they appear not much less frequently for screening [2, 4].

Not only from a medical but also ethical point of view, every doctor should perceive obesity as a chronic disease with a complex etiology that requires treatment. A patient with obesity should be treated with respect, and his/her illness should not be a source of shame and self-blame. A physician should use appropriate medical vocabulary in relation to an obese patient, show empathy towards him/her and give advice appropriate to his/her situation, as well as implement all possible therapeutic procedures, including pharmacotherapy and psychotherapy [2]. The principle of person-centred care should be the norm in the approach to obese patients [5].

Why should obesity be treated during a pandemic?

In Poland, nearly 8 million adults suffer from obesity diagnosed on the basis of the World Health Organisation criteria, and overweight is diagnosed in almost 19 million. Due to the lack of reliable data, estimating the incidence of all chronic obesity complications is extremely difficult. Numerous data confirm that the causal treatment of obesity complications is its effective treatment with the use of all scientifically proven methods, tailored to the individual patient's needs.

The COVID-19 pandemic has proven that the current approach, focused mainly on symptomatic treatment of obesity complications, does not bring the intended results if the patient becomes infected. The inequality in health experienced by obese patients has made them the most vulnerable to severe COVID-19 infection and death thereof.

Data from China, Italy, and the USA showed that obese patients infected with COVID-19 had a longer duration of infection and more often required intensive medical supervision, including intubation and mechanical ventilation. Moreover, obesity and its complications were independent risk factors for hospitalisation and death of the infected [6–9]. It should also be noted that data from a study conducted in New York showed that obesity and its complications caused severe COVID-19 infection and increased the risk of death also among children and adolescents [10].

Overweight in patients with SARS-COV-2 infection increased the risk of developing severe pneumonia by 86%, and obesity by 142% [11]. What are the reasons for this? Obese patients have decreased immunity (chronic systemic inflammatory reaction, increased activation of the hypothalamic-pituitary-adrenal system, low physical activity), they often have obese hypoventilation syndrome (reduced chest volume — disorders of ventilation and perfusion), left ventricular hypertrophy, and sometimes heart failure.

The major complications of obesity also increase the risk of death from COVID-19 (hypertension by 6%, type 2 diabetes by 7.3%, cardiovascular disease by 10.5%, chronic lung disease by 6.3%, and cancer by 5.6%) [12].

It should be emphasised that quarantine in the long term due to exposure to stress may increase people's susceptibility to obesity development, a risk factor for severe COVID-19 infection [13, 14]. It should also be added that the same stressors may have an impact on people not subject to forced quarantine. Food is an easily accessible "stepping stone" from problems; therefore, we are dealing with an increase in the percentage of people who eat under the influence of emotions and those who meet the criteria for the diagnosis of eating disturbances (compul-

sive eating syndrome, night eating syndrome, food addiction) and those with worsening of pre-existing disturbances.

Factors that cause anxiety and sadness at present include the following: adaptation to new functioning conditions, the possibility of infection, illness of relatives — especially the elderly, fear of creating a threat to others, uncertain future in the health and social dimension (it is not known when the pandemic will end and when life will return to normal, it is not known whether the pandemic will not return in the future, fear of what the world will look like after the pandemic, how much we will have to change our lifestyle, our habits, and re-evaluate our dreams, fear of worsening economic situation, loss of job, and collapse financial), social isolation and increasing family conflicts, organisational problems related to remote work and remote learning, limitations in relieving stress outside the home (fear of using fitness clubs, cinemas, theatres, and other entertainment venues, and traveling). Additionally, there is a significant deficit of positive stimuli.

A separate factor influencing weight gain during the pandemic is the reduction in physical activity due to the introduced restrictions and quarantine.

The reward system and the regulation of food intake

The regulation of food intake is a complex process and is not limited to satiety and hunger, which are biological signals controlled by the hypothalamus. Hunger is a physiological feeling of the state of higher organisms related to a lack of food. It is also a contributing impulse to food intake and gaining behaviour. However, satiety inhibits this impulse.

An important role in human food intake is played by the sensation of appetite, which causes the search for a specific food not to satisfy hunger but to feel the pleasure of eating it. Appetite is driven by emotions and is independent of the feeling of satiety. The reward system is responsible for the feeling of appetite [15, 16].

Even in people with normal body mass, stress (the body's reaction to events that disrupt its homeostasis — stressors related to experiencing both negative and positive emotions that exceed our ability to cope effectively) and the associated activation of the hypothalamus-pituitary-adrenal gland axis increases the release of cortisol, reduces the sensitivity of the hypothalamus to the action of leptin, and enhances the influence of the reward system, which is responsible for food intake related not to biological need but to pleasure [17]. Activation of the reward system, including its parts such as the nucleus accumbent, increases the tendency to eat high-energy food high in sugar, fat, and sodium [18]. Stress can lead to eating more food, and with a higher propensity to eat high-energy foods. In addition, stress reduces the tendency to exercise and interfere with sleep. The mechanism of treating food as a reward or consolation arises in infancy or may be established later in life. Overeating can be a way to reduce anxiety and frustration. Many people eat food when the stress factor is unclear and causes a predominant feeling of anxiety. Eating becomes a way to regain self-control over the level of feeling emotions.

Stimulation of dopamine neurons in the ventral tegmental area causes the release of dopamine in the nucleus accumbens. Activation of dopamine receptors causes a feeling of conscious pleasure (prefrontal cortex) and motor activity related to the search for reward (basal ganglia). The hippocampus (memory) and amygdala (emotions) are also activated. The subjective feeling of pleasure is proportional to the amount of dopamine released from the nerve endings in the nucleus accumbens. Tasty food increases dopamine levels by 50%. It can be concluded that reducing dopamine secretion in the structures of the reward system causes the desire/impulse to obtain pleasure, and endogenous opioids increase the feeling of pleasure from, for example, eating [19].

Diagnosis of obesity — should the new criteria be used?

The 1998 diagnostic criteria for overweight and obesity are based solely on body mass index (BMI) values and do not take into account the amount or distribution of adipose tissue in the body or their impact on the patient's health [1]. Data on the impact of overweight and obesity and their complications on the severity of the course and the risk of death from COVID-19 indicate that it is time to revise these archaic criteria and adopt algorithms that can be used in any doctor's office, but taking into account the patient's general health. These conditions are met by the criteria proposed in 2016 by the American Endocrine Societies. On the basis of which we recognise the following:

- overweight degree 0 — BMI 25.0–29.9 kg/m^2 and without complications such as the following: pre-diabetes, type 2 diabetes, dyslipidaemia, arterial hypertension, cardiovascular disease, non-alcoholic fatty liver disease, polycystic ovary syndrome, female infertility, male hypogonadism,

asthma, sleep apnoea syndrome, hypoventilation syndrome, gastroesophageal reflux disease, stress urinary incontinence, osteoarthritis, and depression,
- obesity degree 0 — BMI ≥ 30 kg/m^2 and without the above-mentioned complications,
- first-degree obesity — BMI ≥ 25 kg/m^2 and ≥ 1 mild or moderate complication,
- second-degree obesity — BMI ≥ 25 kg/m^2 and ≥ 1 severe complication [20].

These criteria allow for a much earlier diagnosis of obesity and initiation of treatment, which may significantly improve health or prevent the development of complications. Therefore, we recommend using them.

However, these criteria also do not include the diagnosis of the root cause of the positive energy balance. Proper diagnosis of the cause of obesity development allows the selection of adequate treatment methods and increases its effectiveness. Most of the failures in the treatment of obesity are the result of the wrong approach that proper nutritional education and the strong will of the patient will suffice. The lack of understanding of the role of emotions in influencing food intake and the fact that disorders in the functioning of the reward system make the patient "willing but unable" frustrate both the doctor and the patient, which results in discouragement from undertaking obesity treatment. The view that eating disorders should be diagnosed by a psychiatrist is incorrect because screening is performed using simple diagnostic tools, such as diagnostic criteria:
- compulsive eating syndrome: repeated episodes of uninhibited eating at least once a week for three months and at least three of the following symptoms: eating much faster than normal, eating until you feel uncomfortably full, eating large portions of food without feeling physically hungry, eating alone due to shame/embarrassment in eating, feeling disgusted with oneself, depression or guilt after overeating, as well as a pronounced suffering about the way of eating and the lack of compensatory activities related to it (induction of vomiting, use of diuretics, significant increase in physical activity) [21];
- night eating syndrome: eating ≥ 25% of one's daily amount of food after the evening meal or at night with consciousness at least twice a week for at least three months and at least three of the following symptoms: skipping breakfast due to lack of appetite at least four times a week, a strong need to eat between the evening meal and falling asleep or at night, difficulty falling asleep or waking up from sleep at least four nights a week, the conviction that food is needed as a condition for starting or returning to sleep, frequent worsening of mood in the evening, as well as significant suffering or deterioration in functioning, and the lack of criteria for mental bulimia and seizure syndrome overeating [22];
- food addiction: eating more, or more than intended, persistent desire to eat or unsuccessful attempts to limit food consumption, devoting a large amount of time to eating activities, neglecting social duties and activities, eating food despite negative physical, mental, and social consequences, limiting or abandoning important social, professional, or recreational activities due to food consumption, and the occurrence of withdrawal syndrome [21].

Any doctor should treat eating disorders in cooperation with a psychotherapist. However, it should be remembered that eating under the influence of emotions does not have to meet the criteria for the diagnosis of eating disorders, and it occurs in an even greater group of obese patients than the disorders discussed above. Therefore, patients should be asked about eating under stress, after a stressful situation, in conditions of boredom, or even strong positive emotions.

Obesity treatment — who, when, and how?

The ideal situation would be if an obese patient could be referred to a specialist centre, where he/she would be looked after by an obesitologist in cooperation with a dietitian, psychologist, and physiotherapist. Because there is no coordinated system of obesity treatment in Poland, and its treatment is among the duties of a family doctor and specialist doctors caring for patients diagnosed with obesity complications, it is these groups of doctors who are obliged to diagnose and treat this disease. If the doctor is unable or unwilling to treat obesity, after diagnosing it, he/she should refer the patient to another doctor who will take care of the patient. We suggest that patients be referred to doctors who have obtained certificates of the Polish Association for the Study of Obesity. The list of such people is available on the websites ptbo.edu.pl or certyfikacjaptbo.pl. [23]. It is unethical not to diagnose and treat obesity or to refer the patient to another physician to treat obesity. Obesity is a disease, and referring a patient to a dietitian as the only action without implementing all the necessary therapeutic methods is also an unethical action.

It should be emphasised that four out of five medications registered in the USA for the treatment

of obesity and two out of every three approved in Europe act in the central nervous system. The only drug that acts locally in the gastrointestinal tract is orlistat, a drug of marginal importance in the pharmacological treatment of obesity. Drugs influencing food intake have a pharmacological effect in the CNS, because these are the centres responsible for the feeling of satiety, hunger, and appetite. However, this does not provide sufficient justification for the drugs registered to support obesity treatment to be prescribed only by a psychiatrist, and even less so that only a psychiatrist can diagnose eating disturbances

Obesity is a progressive disease, and the development of its complications depends on the distribution of adipose tissue, the stage of the disease, and its duration. In order to prevent the progression of the disease and the development of complications, treatment of obesity should be started as early as possible at the stage of overweight degree 0. It should also be undertaken at any other stage of the disease, without waiting for the development of complications.

The overarching goal of obesity treatment is to inhibit the progression of the disease, avoid recurrences, prevent the development of complications caused by excess body fat or reduce their severity, improve the overall health and quality of life of the patient, and extend their life. To achieve this goal, different percentages of body mass reduction from baseline may be needed in different patients [23].

In order to prevent obesity complications, the initial goal is a reduction of 5–10% of the initial body mass over a 3–6-month period, then the same maintenance period, followed by another 5–10% reduction in body mass. The main goal in patients without obesity complications is to reduce the severity of the disease by one degree. On the other hand, in patients with complications, the overriding goal is to achieve a weight reduction that will significantly improve the control of this complication, the possibility of reducing the number or doses of drugs used due to the complication or discontinuing their use, and in some cases achieving remission in terms of the complication [23].

In the treatment of obesity, unlike slimming, the goal is not to lose weight quickly and significantly, but to reduce it slowly and over the long term, which will improve health and quality of life, and increase life expectancy. Therefore, the methods used in the treatment of obesity, including pharmacotherapy, are to cause a slow loss of body mass. This should be carefully explained to the patient, because the result may not match their expectations, which must be verified, and the new goal must be accepted by the patient. The goal assigned to the patient must be specific, measurable, acceptable, realistic, and timely (SMART). On the way to the final goal, it is necessary to set sub-goals and short-term goals ranging from three to six months [23].

As already mentioned, the selection of obesity treatment methods must be individualised, taking into account, first of all, the root cause of a disturbed energy balance. It should be remembered that this treatment is a long-term process.

In the treatment of overweight and obesity, the doctor should follow the 5A rule:

- ASK — explaining to the patient the essence of the disease and its consequences and assessing his/her readiness to change,
- ASSESS — assessment of health, causes of weight gain, and the occurrence of complications caused by excess fat in the body,
- ADVICE — presenting treatment options that can be applied to a specific patient,
- AGREE — obtaining the patient's consent for the proposed therapeutic goal and treatment plan,
- ASSIST — supporting the patient in the therapeutic process [24].

The basis of treatment of overweight and obesity is to obtain a negative energy balance by changing eating habits and increasing physical activity. However, it should be remembered that in patients with an emotional background of increased food consumption, nutritional education itself may be counterproductive; we should remember that such a patient really wants to do this but is unable to. Their brain calls to eat and the fact that he/she does not follow the recommendations is not his/her fault. The role of the doctor is to help such patients through the use of appropriate pharmacotherapy, in some cases also prescribing psychotherapy.

Surgical treatment in patients with an emotional background of increased food consumption should be recommended with caution, and pharmacological and psychological support should be taken into account both during the preparation for surgery and after its performance [25].

Individual selection of pharmacotherapy based on the mechanisms of drug action and the causes of obesity — monotherapy positioning, use of polytherapy

Currently, there are three drugs available in Poland to support the treatment of overweight and obesity:

- orlistat (gastrointestinal lipase inhibitor) is used only in the group of patients who prefer fat-

ty foods and have no problems controlling the amount of food consumed (it does not affect the feeling of satiety and appetite). In view of current knowledge on the importance of emotions in the regulation of food intake, this drug is of marginal importance and therefore has not been included in the current guidelines;

- a combination medicinal product containing two active substances: bupropion hydrochloride and naltrexone hydrochloride, reduces food intake by increasing satiety and inhibiting eating under the influence of emotions (appetite). This drug acts synergistically on the neurons of the arcuate nucleus of the hypothalamus. The active substances contained in the drug increase the secretion of proopiomelanocortin of the α-melanotropin precursor (α-MSH) (bupropion — stimulation of the feeling of satiety) and prolong its release by blocking the mi opioid receptor (naltrexone — prolonging the feeling of satiety). Moreover, bupropion, by inhibiting dopamine reuptake in the synapses of the mesolimbic reward system, and naltrexone, by blocking opioid receptors, reduce appetite. Thus, this drug acts on both the biological and emotional mechanisms of food intake, which facilitates the patient's implementation of recommendations regarding changes in eating habits [15, 26];
- liraglutide, a long-acting GLP-1 receptor analogue, increases the glucose-dependent insulin secretion from pancreatic β-cells (1.8 mg/day used in the treatment of type 2 diabetes). Moreover, liraglutide, acting on the centres of satiety and hunger in the hypothalamus, stimulates the feeling of fullness and inhibits the feeling of hunger. This drug does not affect food intake related to emotions; that is the appetite [27].

In accordance with the recommendations of the American Endocrine Associations, short-term (3–6 months) pharmacological treatment of obesity has not shown long-term health benefits in clinical trials and is not recommended. It is also recommended that chronic use of pharmacotherapy be considered due to the chronic nature of the disease. The selection of pharmacotherapy should be individualised [20]. The current guidelines also recommend this approach to the use of pharmacotherapy supporting the treatment of obesity.

We recommend that pharmacotherapy be offered to everyone who is overweight or obese if there are no contraindications to its use.

It is worth remembering that WHO diagnostic criteria based solely on BMI values do not properly reflect the stage of the disease. The new diagnostic criteria of the American Endocrine Societies of 2016 also take into account the occurrence of complications caused by excess fat in the body [20]. In each case of complications caused by excess body fat, in the treatment of which the causative treatment is to achieve weight loss, and in each case of eating under the influence of emotions or low mood, especially if it is accompanied by low self-esteem, the simultaneous implementation of lifestyle changes and pharmacotherapy should be considered.

Individual selection of pharmacotherapy should be based on the identified an etiological factors that led to the development of the disease. As already mentioned, the causal treatment of obesity is the basis for the effective treatment of its complications. The archaic approach of putting the complications of obesity rather than its causes in the selection of pharmacotherapy should be abandoned. Failures in obesity treatment are the result of this approach. Current knowledge indicates that in the selection of pharmacotherapy of complications, obesity should be taken into account as a cause, and in the selection of pharmacotherapy of obesity, factors causing a positive energy balance should be taken into account.

Based on the data from available studies on the aetiology of the disease, as well as efficacy and safety, we recommend the following criteria for selecting pharmacotherapy:

1. Due to its mechanism of action, efficacy, and safety, the drug considered as a first-line drug should be a combined preparation containing bupropion and naltrexone (Mysimba®).
2. Liraglutide in a dose of 3 mg (Saxenda®) should be considered as a second-line drug in a situation where eating under the influence of emotions is excluded (reaching for food in situations of experiencing negative and positive emotions and boredom, eating disorders: compulsive eating syndrome, night-time syndrome, addictive eating) and depressed mood or there are persistent contraindications to the use of the first-line drug.
3. The use of polytherapy with a combination product of bupropion and naltrexone and liraglutide should be considered in patients with impaired carbohydrate metabolism with associated emotional eating. In this case, the dose of liraglutide used should be selected individually (1.8 mg Victoz® or 3.0 mg Saxenda®) depending on whether only type 2 diabetes or obesity is considered as the indication for the use of liraglutide.
4. Liraglutide doses lower than 3.0 mg daily and other active substances not approved for the treatment of overweight and obesity in monotherapy should not be recommended in monotherapy.

Justification of the above recommendations

1. Emotional eating is the most common cause of noncompliance with the recommendations for changing eating habits; the patient wants to but cannot. The use of pharmacotherapy, which does not affect the reward system, does not bring the expected results, increases frustration, and promotes eating. Not all emotional eating can be diagnosed as an eating disturbance. Emotions triggering eating can vary in nature, including tension and fear, but also boredom. The prevalence of eating disorders among obese patients is estimated at 40–70%, but this can be greatly underestimated because they are rarely diagnosed.
2. Both drugs act centrally, but only the combination of bupropion with naltrexone, by acting on the reward system, suppresses appetite and thus eating under the influence of emotions, additionally improves the mood [28]. Isolated studies suggesting an effect of liraglutide on the reward system come from animal studies. In a study using functional magnetic resonance imaging in a group of 20 patients treated for five weeks with liraglutide 5.0 mg or placebo no differences in the response of reward system areas to food images were found between the study groups [29]. The choice of the combination of bupropion and naltrexone as the first-line drug proposed in this document and liraglutide as the second-line drug is not a common recommendation in many existing documents and expert group positions. It may therefore arouse polemics on the part of other experts. However, this position proposes such a prioritization of these drugs also due to the greater acceptance of the form of oral treatment (first-line treatment) than of subcutaneous injections (second-line treatment) and the fact that obese patients more often require therapy affecting the function of the reward system, which helps in dealing with situations where emotions are the cause of consuming excess energy. In addition, experts suggested similar solutions (first-line drug — Mysimba®, second-line drug — Saxenda®) recently adopted in the current treatment and reimbursement regimens in Norway and Denmark. Perhaps, the emergence of other effective oral medications for the treatment of obesity, as well as new research, will require our opinion to change in the future.
3. The combination of bupropion with naltrexone has a better safety profile. A comparative analysis showed that the number needed to harm (or the number of people in treatment during the year who experience side effects) is 1 in 17 with bupropion and naltrexone in combination and 1 in 4 with liraglutide. Therefore, side effects occur more than four times often during the use of liraglutide [30].
4. Efficacy: a total of 12,868 patients participated in the clinical trials of bupropion and naltrexone combination COR III phase and LIGHT IV phase, with a weight loss of at least 5% at baseline in 53–80% (depending on the study) for 56 weeks, and 10% in 26–55% [31–35]. In contrast, the phase III SCALE trials, which involved a total of 5358 patients for 56 weeks, achieved a weight loss of at least 5% at baseline in 63.2% of patients treated with 3.0 mg, and 10% in 33.1% [36–39].
5. The cardioprotective effect of liraglutide and the reduction of the risk of death from cardiovascular causes were observed only in the group of patients with type 2 diabetes (LEADER study) [40]; there were no such data in other obesity groups. The LEADER study used the approved dose of liraglutide for diabetes (1.8 mg/day), not the approved obesity dose (3.0 mg). The results of these studies cannot be extrapolated to the entire population, nor the fact that liraglutide prolongs life expectancy. The LEADER study included patients with known cardiovascular disease and people with cardiovascular risk factors. Subgroup analysis suggests that the cardiovascular benefit of liraglutide was primarily in the subgroup of patients with known cardiovascular diseases in which specific cardiovascular benefits were previously seen. In contrast, a study to evaluate lixisenatide in acute coronary syndrome (ELIXA) showed no cardiovascular benefit from its use in patients with type 2 diabetes and recent acute coronary syndrome. In the ELIXA study, no such group differences with regard to cardiovascular medications were found. Perhaps some of the cardiovascular benefits that were observed in the LEADER study were due to differences in standard of care rather than the use of liraglutide. Multivariate analyses should be carried out, which would at least partially explain these doubts [41]. Post hoc calculations, which are based on the actual sample size, indicate that the sample power for the observed superiority was 75.5%, which is well below the previously planned 90% power for non-worse. Thus, this lack of power raises concerns about the type I error of superiority [42]. The reduction in HbA_{1c} levels with liraglutide was modest and other factors, such as weight loss, may have contributed to the benefits seen with liraglutide [43]. A high propor-

tion of patients enrolled in these studies had previously experienced a CVD adverse event; therefore, this therapy is assessed mainly as a secondary prevention of subsequent CVD events. This cannot be fully translated into primary prevention. These studies provide reassuring evidence that the new glucose lowering drugs do not adversely affect CVD events, and some of these drugs may reduce their risk [44]. In the LEADER study, the primary endpoint incidence was 13.0% lower with liraglutide than with placebo. There was also a 22% lower CVD death rate and a 15% reduction in all-cause deaths. The number of patients needed to treat (NNT) to prevent one cardiovascular event in three years was 66 and to prevent death from any cause was 98 [45]. It has also been shown that the benefits of liraglutide appear to be limited to a predetermined subgroup of people with known cardiovascular disease. Therefore, the conclusions and implications of the LEADER study are currently limited to the group with type 2 diabetes at high cardiovascular risk [46]. Experts emphasize that our comments and doubts concern only the unauthorized extrapolation of the LEADER study results to the obese patient population. However, they do not undermine the importance of this study for contemporary diabetology and current antidiabetic treatment algorithms, especially in patients at high cardiovascular risk.

6. There are no comparative studies assessing the time it takes for the drugs to take effect.

The use of telemedicine techniques in the treatment of obesity in the pandemic era and in the future

Currently, in providing remote advice, telephone contact or instant messaging is most often used. However, more and more often telemedicine applications using artificial intelligence algorithms are used. Such solutions are already used in psychiatry. Psychiatrists were also the first to provide recommendations for tele-visiting during a pandemic. According to these recommendations, the conversation with the patient should begin with the assessment of the patient's anxiety related to the epidemic, reassuring him/her and supporting him/her in drawing appropriate conclusions and correcting the information chaos he/she was subjected to. After the patient has calmed down, move on to his/her current health problem. Questions should not be left unanswered, and the patient should be able to contact remotely if necessary [47].

The sanctioning of the place of tele-visiting in the NHF system allowed help to be provided for many patients during the closure of health care facilities due to the pandemic, it also facilitated the introduction of e-prescriptions.

The combination of traditional counselling and televisiting can be an effective tool for diagnosing and treating obesity when there is no time at the clinic. Moreover, the inclusion of telemedicine in the care of obese patients may contribute to the improvement of the doctor-patient relationship and the patient's compliance with the recommendations, including those related to pharmacotherapy. Prior to March 2020, GPs provided sporadic telephone consultations. Before 2019, this type of advice was not sanctioned by the National Health Fund. Medical tele-visit was introduced by the Regulation of the Minister of Health of October 31, 2019, amending the regulation on guaranteed benefits in the field of primary health care Journal of Laws 2019 item 2120. The provisions came into force on November 5, 2019. The regulation specifies the issue of providing services in outpatient conditions, but also as part of night health care, indicating that remote assistance is possible via teleinformation systems or telephone communication. Thanks to this, the patient has the right to tele-visit.

From January 2020, at least once a year, the family doctor should take anthropometric measurements and assess the nicotine status of each patient reporting to the primary health care practice (new requirement of the National Health Fund — Order of the President of the National Health Fund No. 177/2019 / DSOZ).

Currently, in 2020, the National Health Fund additionally finances the care of patients chronically suffering from diabetes, cardiovascular diseases, or thyroid gland conditions. Most of these patients are also obese. It is advisable that obesity should also be included as a chronic disease in the list of causes of medical consultations qualifying for additional financing by the National Health Fund. Until the new regulations are in place in the GP surgery, advice on obesity may be part of the follow-up advice on chronic diseases. A family doctor who has appropriate knowledge about obesity and drugs supporting its treatment has an ethical duty to treat obesity and propose pharmacotherapy to the patient. In order to increase the knowledge of doctors, current guidelines have been developed.

During the pandemic, tele-visit were also used and reimbursed in specialist counselling.

Telemedicine in the form of the use of medical applications in the treatment of obesity is a new formu-

la for supporting behavioural and pharmacological therapy. These applications can support the doctor both in the diagnostic process and in making therapeutic decisions, and support treatment through various forms of increasing therapeutic adherence, digital forms of treatment, and monitoring the patient's condition between meetings or tele-meetings with the doctor. Contact between a doctor, dietitian, or psychologist with the patient should be in the form of video-visits, enabling the establishment of eye contact, assessment of the patient's facial expressions and pantomimics as well as establishing contact and a therapeutic relationship.

Telemedicine applications can be particularly useful in increasing therapeutic adherence. Low therapeutic adherence of obesity patients is the cause of incomplete treatment effectiveness, side effects of drugs, and in the long term, somatic and psychological complications of obesity, hospitalisation, and increased treatment costs. The reason for low therapeutic adherence is usually false and inadequate beliefs about obesity, rationalising and contradicting it, beliefs about the ineffectiveness of drugs or the presence of their side effects, or the lack of patient resources (e.g. lack of economic resources to buy drugs or forgetting to take a drug). All these reasons should be taken into account when creating remote telemedicine obesity treatment algorithms.

Telemedicine applications use various methods to support therapeutic adherence that can be used in the treatment of obese patients. Those are:

- reminders in the form of text messages and smartphone notifications,
- video education on the disease and drugs,
- obesity support groups in communities in the Internet environment,
- point systems that strengthen the habit of taking medication,
- video meetings with a doctor, psychotherapist, or dietician.

Improving drug compliance and the effectiveness of obesity treatment using telemedicine tools requires a comprehensive approach to the entire treatment process, not only focusing on therapeutic adherence. In constructing telemedicine obesity therapy, it is advisable to take into account the following recommendations:

Creation and development of user-friendly telemedicine applications enabling full visual-auditory and safe video-connection with the patient.

Creation, research, and popularisation of telemedicine applications for effective stress reduction as a supporting method in the treatment of obesity. Medical applications can thus offer an alternative strategy to deal with negative emotions in relation to food. In reduction of stress in patients treated for obesity can use virtual reality, augmented reality, breathing training, therapeutic games, and prohealth musical frequencies.

Such applications offer great hope for more effective obesity treatment in the near future.

Summary

Treating obesity in the pandemic era is more important than ever. The current situation is conducive to the development of new diseases and disease worsening, mainly as a result of compensating for negative emotions by eating. Taking into account the data on the impact of obesity and its complications on the severity of the course and the risk of death due to COVID-19, we recommend using the 2016 American Endocrine Society's criteria for the diagnosis of obesity instead of the 1998 WHO criteria. We also recommend diagnosis of eating under the influence of emotions and the occurrence of eating disturbances such as compulsive eating syndrome, night eating syndrome and addictive eating, and the occurrence of obesity complications. It is also advisable to diagnose family members towards overweight and obesity and to involve them in helping the patient.

The approach to treatment should be individualised and should not be limited to nutritional and physical activity education. Each patient should be offered appropriately selected pharmacotherapy, and, if necessary, also psychotherapy. The first-line drug should be a combined preparation containing naltrexone and bupropion (Mysimba®). Liraglutide in a dose of 3 mg (Saxenda®) should be considered as a second-line drug in a situation where eating under the influence of emotions is excluded (reaching for food in situations of experiencing negative and positive emotions and boredom, eating disturbances: compulsive eating syndrome, night eating syndrome and addictive eating), depressed mood, or there are persistent contraindications to the use of the first-line drug.

It is unethical not to treat obesity or refer the patient to another doctor who will treat it. The use of telemedicine tools can facilitate work in therapeutic teams (doctor, dietitian, psychotherapist), as well as improve patient compliance with pharmacotherapy recommendations and changes in eating habits and the level of physical activity. To facilitate the application of the above guidelines in practice, an algorithm for the diagnosis and treatment of obesity using telemedicine techniques has been developed (Fig. 1).

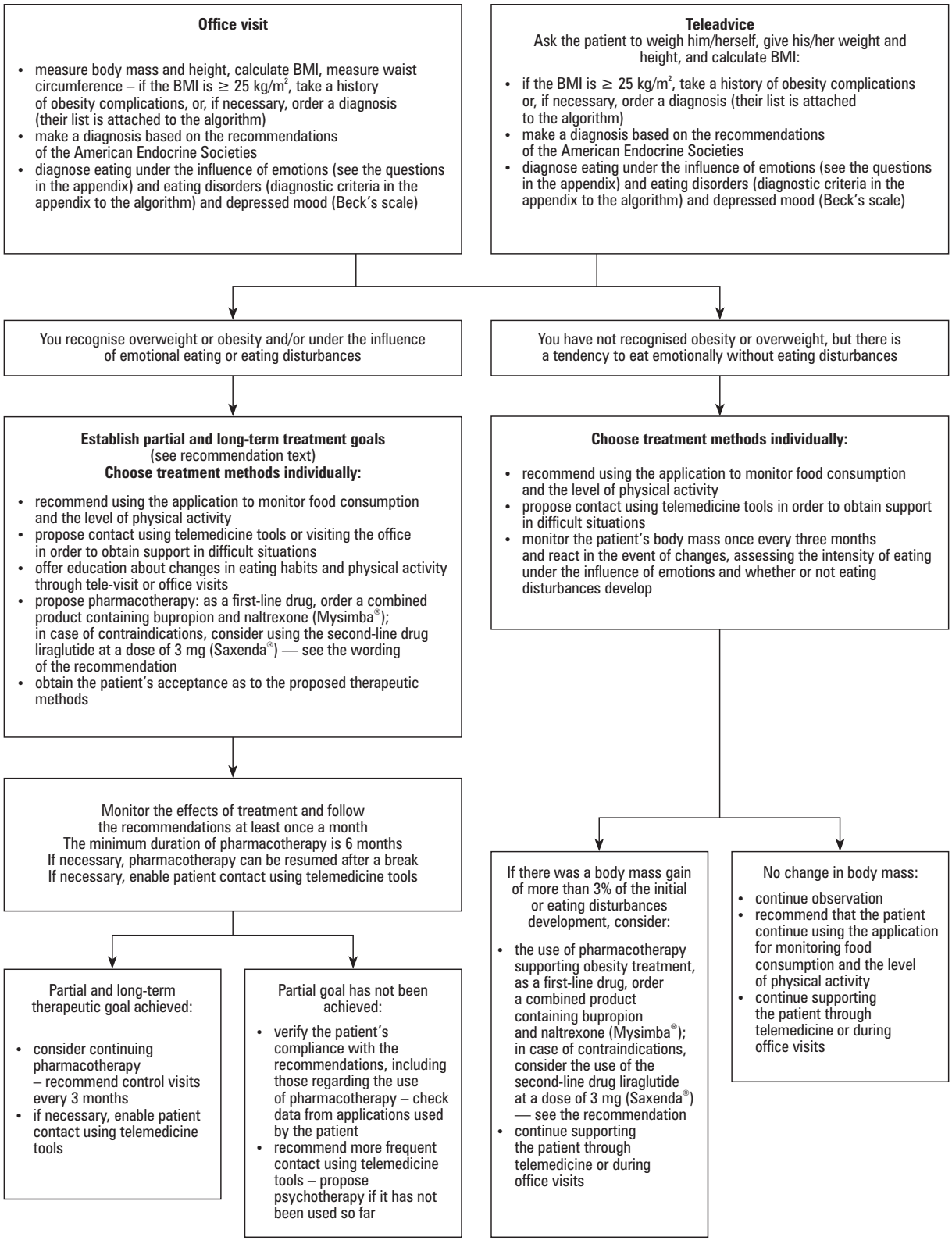

Figure 1. Algorithm for diagnosing and treating obesity using telemedicine techniques

List of obesity complications that should be included in the history or their diagnosis should be implemented, if not previously performed: prediabetes, type 2 diabetes, dyslipidaemia, hypertension, cardiovascular disease, non-alcoholic fatty liver disease, polycystic ovary syndrome, impaired fertility in women, hypogonadism in men, asthma, sleep apnoea syndrome, hypoventilation syndrome, gastroesophageal reflux disease, stress urinary incontinence, osteoarthritis, depression

Eating under the influence of emotions: reaching for food during or after a stressful situation caused by both positive and negative factors, eating when feeling anxious, rewarding yourself with food, eating when something has failed — comforting with food, eating in situations of boredom, eating in in order to reduce the feeling of fatigue
Ask the patient: Do you feel stomach suction in stressful or anxious situations? Does stress make you reach for food? Do you feel like eating after a stressful situation? Success is food? When something has not turned out, do you reach for food? When you are bored, do you reach for food? Do you use food during other activities, e.g. reading, watching TV, working? Do you reach for food while using the computer? When you feel tired, does eating help to reduce this feeling?

Binge eating syndrome: repeated episodes of unrestrained eating at least once a week for three months, and at least three of the following symptoms: eating much faster than normal, eating until you feel uncomfortably full, eating large amounts of food without feeling physically hungry, eating alone due to embarrassment/embarrassment in eating, feeling disgusted with yourself, depressed or guilty after overeating, as well as marked suffering from eating habits and lack of compensatory activities associated with it (inducing vomiting, using diuretics, increasing physical activity significantly)

Night eating syndrome: eating min. 25% of the daily food ration after the evening meal or at night with awareness at least twice a week for at least 3 months and at least three of the following symptoms: skipping breakfast due to lack of appetite at least 4 times a week, a strong need to eat between the evening meal and falling asleep or at night, difficulty falling asleep or waking up from sleep at least 4 nights a week, the conviction that food is needed as a condition for starting or returning to sleep, frequent worsening of mood in the evening, as well as significant suffering or deterioration of functioning and lack of criteria for psychological bulimia and the binge eating syndrome

Addictive eating: eating more or more than intended, persistent desire to eat or unsuccessful attempts to limit food consumption, devoting a lot of time to eating activities, neglecting social responsibilities and activities, eating food despite negative physical, mental, and social consequences, limiting or abandoning due to eating important social, professional or recreational activities, and the occurrence of withdrawal syndrome

Figure 1. Algorithm for diagnosing and treating obesity using telemedicine techniques

We hope that it will be a helpful tool to facilitate everyday work and will result in more patients being properly diagnosed and effectively treated.

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Severity of SARS-COV-2 infection and angiotensin converting enzyme inhibitors and angiotensin receptor blockers: a meta-analysis

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Abstract

Background: The mechanism of entry of SARS-CoV-2 into the human host cell is through the ACE2 receptor. During the pandemic, a hypothesis has been proposed that angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) could be risk factors for the development of severe SARS-CoV-2 infection. The objective of the study was to conduct a meta-analysis of the association between ACEI or ARB use and SARS-CoV-2 infection severity or mortality.

Material and methods: We searched PubMed, EMBASE, Google scholar and the Cochrane Database of Systematic Reviews for observational studies published between December 2019 and August 4, 2020

Studies were included if they contained data on ACEI or ARB use and SARS-CoV-2 infection severity or mortality. Effect statistics were pooled using random-effects models. The quality of included studies was assessed with the Newcastle–Ottawa Scale (NOS).

Data on study design, study location, year of publication, number of participants, sex, age at baseline, outcome definition, exposure definition, effect estimates and 95% CIs were extracted.

Results: Twenty-six studies (21 cohort studies and 5 case-control studies) were identified for inclusion, combining to a total sample of 361467 participants. Mean age was 61.48 (SD 8.26) years and 51.63% were men. The mean NOS score of included studies was 7.85 (range: 7–9). Results suggested that ACEI or ARB use did not increase the risk of severe disease or mortality from SARS-CoV-2 infection (OR = 0.88, 95% CI: 0.75–1.02, p > 0.05).

Conclusions: At present, the evidence available does not support the hypothesis of increased SARS-CoV-2 risk with ACEI or ARB drugs.

Key words: SARS-CoV-2; COVID-19; angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors; renin–angiotensin system (RAS)

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Introduction

It had not been anticipated that a phenomenon such as the appearance of the new SARS-CoV-2 pandemic would affect the world in such a short time and lead to serious health and economic consequences. Scientists around the world are in a race against time in the search for effective treatment approaches. Among the many questions that need urgent clarification is that of the possible drug-disease interactions in patients taking angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs). These are among the most widely used antihypertensive drug classes in the world [1].

The renin–angiotensin system (RAS) has the function of maintaining homeostasis of blood pressure, fluid and salt in the human body. The renin–angiotensin system contains two homologous enzymes belonging to the angiotensin converting enzyme (ACE) dipeptidyl carboxypeptidase family, with different functions: the angiotensin I converting enzyme 1 (ACE1) converts angiotensin I to angiotensin II; and the angiotensin I converting enzyme 2 (ACE2) decreases the level of angiotensin II and negatively regulates the RAS system. Thus, ACE2 reduces the effects of vasoconstriction, sodium retention and fibrosis. ACE2 is expressed in various organs such as the heart, kidneys and especially in alveolar epithelial cells of the lung [2]. Under normal conditions, circulating levels of soluble ACE2 are low and its function at the lung level is minimal [3].

The mechanism of entry of SARS-CoV-2 into the human host cell is through the ACE2 receptor. SARS-CoV-2 has an envelope made up of glycoproteins, called S1 (Spike) and S2, the former binding to ACE2 on the cell surface and the latter with the cell membrane [4]. While this mechanism is similar to that of another coronavirus that caused the SARS epidemic in 2002–2003 [5, 6], SARS-CoV-2 has a higher affinity for ACE2 [7]. Although their three-dimensional structure is similar, SARS-CoV and SARS-CoV-2 differ in about 28% of the amino acid sequence in the receptor binding domains; SARS-CoV-2 has a distinct loop with flexible glycyl residues replacing rigid prolyl residues, which makes its structure less rigid and may explain its greater affinity for the ACE2 receptor [7]. Angiotensin I converting enzyme 2 was involved in the pathophysiology of SARS-CoV infection [8] and it is feared that in SARS-CoV-2 infection, this effect could be of greater magnitude. In addition, prior to the pandemic it had been reported that ACEIs/ARBs could increase mRNA expression of ACE2 at the cardiac level [9]. Hence, it has been hypothesized that ACEIs and/or ARBs could be risk factors for the development of severe forms of SARS-CoV-2 infection [10, 11]. In the midst of the COVID-19 pandemic crisis, this simple hypothesis was, without clinical or research evidence to support it, widely disseminated by the media, which in turn caused great concern to patients who were taking these medications. Official statements rapidly followed recommending that these medications continue to be taken [12] in view of the absence of evidence to support the hypothesis. However, the absence of evidence does not mean evidence of absence and there is still an urgent need for clarification. In that light, we conducted a meta-analysis of the association between ACEI or ARB use and SARS-CoV-2 infection severity or mortality.

Material and methods

This study was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [13].

Search strategy

Two independent investigators performed a systematic search in PubMed, EMBASE, Google scholar and the Cochrane Database of Systematic Reviews for observational studies published between December 2019 and August 4, 2020. In addition, we conducted a secondary search based on the reference list of retrieved articles. The PubMed search strategy is detailed in Supplementary Table A.

Eligibility criteria

We searched for randomized controlled trials (RCTs) or observational studies reporting data on ACEI or ARB use and SARS-CoV-2 infection severity or mortality. We included studies in English or other languages (all ages) meeting the following criteria: a) COVID-19 patients were diagnosed according to the interim guidance of the World Health Organization [14]; b) the study presented data on hazard ratios (HRs), relative risks (RRs), or odds ratios (ORs) with confidence intervals (CIs) or offered enough data to allow these to be calculated (including via email correspondence with original authors if necessary); and c) SARS-CoV-2 infection severity criteria were described.

Quality assessment

The quality of observational studies (cohort and case-control studies) and RCTs were assessed according to the Newcastle-Ottawa Quality Assessment Scale (NOS) [15] and the Cochrane Risk of Bias

Assessment Tool [16], respectively. Two investigators evaluated the quality of the studies independently. Conflicting results were resolved by discussion and involvement of a third reviewer if necessary.

Data extraction

The following data were extracted from each study: authors, study location, year of publication, study design, number of participants, sex, age at baseline, outcome definition, exposure definition, effect estimates and 95% CIs.

Statistical analyses

Primary analyses evaluated the association (HRs, RRs or ORs) between use of ACEI or ARB and SARS-CoV-2 infection severity or mortality. We used random effects with an inverse variance method to calculate the pooled RRs and 95% CIs according to the heterogeneity between studies [17]. The overall estimates in the pooled analysis were obtained using Meta XL (www.epigear.com) add-in for Microsoft Excel.

Results

After screening 3781 citations, 26 studies (21 cohort studies and 5 case-control studies) were included (Fig. 1) [18–44], combining to a total sample of 361467participants. The characteristics of included studies are summarized in Table 1. Thirteen studies were from China, 8 from USA and the other five being from Belgium, Italy, South Korea, Turkey and UK. Overall, mean age was 61.5 (SD 8.3) years and 51.6% were men. The mean NOS score of included studies was 7.9 (range: 7–9). The outcomes reported in the included studies are presented in Table 1.

For the meta-analysis, we used the combined outcome of severe disease and/or mortality. As shown in Figure 2, the meta-analysis suggested that ACEI or

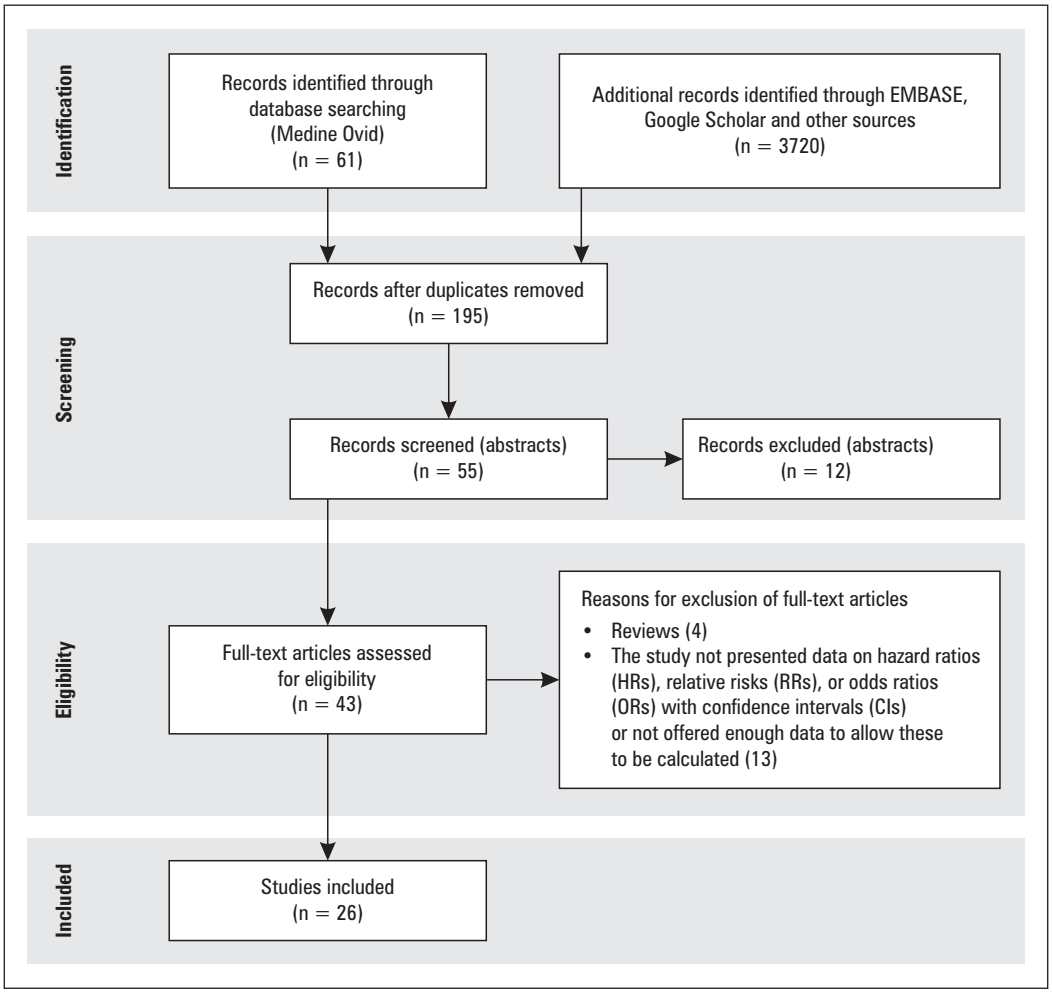

Figure 1. Flowchart of included studies

Table 1. Characteristics of the 26 studies included in the meta-analysis

Author	Country	Study design	Total sample	Mean age	Sex Male (%)	Outcome	Type of RAS inhibitor	NOS	Comorbidities
Guo T. et al. (2020)	China	Cohort	186	58.5	48.7	Mortality	ACEI/ARB	8	Hypertension (33%) Coronary heart disease (11%) Cardiomyopathy (4%) Diabetes mellitus (15%) COPD (2%) Malignant neoplasm (7%) Chronic kidney disease (3%)
Liu Y. et al. (2020)	China	Cohort	511	65	55.1	Severe disease	ACEI ARB	8	Hypertension (100%)
Peng Y. et al. (2020)	China	Cohort	112	62	47.32	Mortality	ACEI/ARB	8	Hypertension (82%) Coronary heart disease (55%) Heart failure (36%) Diabetes mellitus (21%)
Meng J. et al. (2020)	China	Cohort	417	64.5	57.1	Severe disease/ /mortality	ACEI/ARB	8	Hypertension (100%)
Bean D. et al. (2020)	UK	Cohort	205	62.95	51.7	Severe disease/ /mortality	ACEI ARB	7	Hypertension (51%) Diabetes mellitus (30%) and ischaemic heart disease or heart failure (15%)
Yang G. et al. (2020)	China	Cohort	462	67	49.4	Severe disease/ /mortality	ACEI/ARB	9	Hypertension (100%) Diabetes mellitus (30%) Respiratory disease, cardiopathy (18%) Neurological disease (8%)
Feng Y. et al. (2020)	China	Cohort	476	53	56.9	Severe disease	ACEI/ARB ARB ACEI	8	Hypertension (24%) Cardiovascular disease (8%) Diabetes mellitus (10%) Malignancy (3%) Cerebrovascular disease (4%) Immunosuppression (2%) COPD (5%)
Feng Z. et al. (2020)	China	Cohort	564	47	50.4	Severe disease	ACEI/ARB	8	Hypertension (15%) Diabetes mellitus (8%) Cardiovascular disease (4%) COPD (3%) Hepatitis B/C infection (2%) Cerebrovascular disease (1%)
Rentsch C. et al. (2020)	USA	Cohort	585	66.1	95.4	Severe disease	ACEI/ARB ARB ACEI	7	Asthma (8%) Cancer (15%) Chronic kidney disease (15%) COPD (26%) Diabetes mellitus (33%) Hypertension (65%) Liver disease (12%) Vascular disease (29%)
Zeng Z. et al. (2020)	China	Cohort	274	60	45	Mortality	ACEI/ARB	8	Hypertension (100%) COPD (6%) Chronic renal insufficiency (2%) Cardiovascular disease (11%) Diabetes mellitus (15%) Cerebrovascular disease (8%)
Zhang P. et al. (2020)	China	Cohort	1128	64	53.2	Mortality	ACEI/ARB	7	Hypertension (100%) Diabetes mellitus (23%) Coronary heart disease (15%) Chronic renal diseases (4%) Cerebrovascular diseases (3%)

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Table 1. Characteristics of the 26 studies included in the meta-analysis

Author	Country	Study design	Total sample	Mean age	Sex Male (%)	Outcome	Type of RAS inhibitor	NOS	Comorbidities
Li J. et al. (2020)	China	Cohort	1178	55.5	46.3	Mortality	ACEI/ARB ARB ACEI	9	Hypertension (100%) Cerebrovascular disease (19%) Coronary heart disease (17%) Heart failure (3%) Diabetes mellitus (35%) Digestive disorder (22%)
Choi H. et al. (2020)	South Korea	CC	1585	63	42.7	Severe disease/ /mortality	ACEI/ARB	8	Hypertension (100%) Diabetes mellitus (47%) Major neurologic diseases (28%) Chronic lung diseases (19%)
Hu J. et al. (2020)	China	CC	149	57	59.06	Severe disease	ACEI/ARB	7	Diabetes mellitus (20%) Heart disease (5%) COPD (1%) Chronic liver disease (6%) Chronic renal disease (4%) Cancer (2%)
Zhou X. et al. (2020)	China	CC	110	57.7	54.5	Mortality	ACEI/ARB	7	Hypertension (33%) and diabetes mellitus (10%) Cardiovascular disease (9%) Chronic liver disease (4%) Malignancy (4%)
Huang Z. et al. (2020)	China	Cohort	50	52.65	54	Severe disease/ /mortality	ACEI/ARB	8	Diabetes mellitus (13%) Coronary artery disease (3%) COPD (5%) Chronic obstructive pulmonary disease (5%)
De Spiegeleer A. et al. (2020)	Belgium	Cohort	154	86	33.1	Severe disease	ACEI/ARB	8	Hypertension (25%) Diabetes (18%)
Ip A. et al. (2020)	USA	Cohort	1129	Missing	Missing	Mortality	ACEI/ARB ARB ACEI	7	Hypertension (100%)
Khera R. et al. (2020)	USA	Cohort	10196	69	45.4	Mortality	ACEI ARB	8	Hypertension (100%) Diabetes without complications (51%) Myocardial infarction (5%) Chronic heart failure (31%) Chronic pulmonary disease (39%)
Reynolds H. et al. (2020)	USA	Cohort	12594	49	41.5	Severe disease	ACEI/ARB ARB ACEI	9	Hypertension (35%) Heart failure (6%) Myocardial infarction (4%) Diabetes (18%) Chronic kidney disease (10%) Obstructive lung disease (15%)
Richardson S. et al. (2020)	USA	Cohort	5700	63	60.3	Mortality	ACEI/ARB	9	Hypertension (57%) Obesity (42%) Diabetes mellitus (32%)
Chaudhri I. et al. (2020)	USA	Cohort	300	59.1	60	Severe disease	ACEI/ARB	7	Hypertension (44%) Diabetes mellitus (25%) and/or heart failure (15%)
Dublin S. et al. (2020)	USA	Cohort	322044	51	46	Severe disease	ACEI/ARB	7	

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Table 1. Characteristics of the 26 studies included in the meta-analysis

Author	Country	Study design	Total sample	Mean age	Sex Male (%)	Outcome	Type of RAS inhibitor	NOS	Comorbidities
Felice et al. (2020)	Italy	CC	133	73.1	28	Mortality	ACEI/ARB ARB ACEI	8	Hypertension (100%) Chronic heart failure (18%) Diabetes mellitus (26%) Cancer (16%) Chronic obstructive pulmonary disease (11%)
Lam K. el al. (2020)	USA	CC	614	68	56.4	Mortality	ACEI/ARB	8	Hypertension (100%) Diabetes (41%) Asthma (5%) Coronary heart disease (24%) COPD (13%) Heart failure (13%) Cancer (12%) Chronic kidney disease (16%)
Senkal N. et al. (2020)	Turkey	Cohort	611	63	53.2	Severe disease	ACEI ARB	8	Diabetes mellitus (41%) COPD/asthma (14%) Coronary artery disease history (26%) Congestive heart failure (9%)

ACEI — angiotensin-converting enzyme inhibitor; ARB — angiotensin II receptor blocker; SD — standard deviation; CI — confidence interval; RAS — renin–angiotensin system; NOS — Newcastle-Ottawa Scale; CC — case control; COPD — chronic obstructive pulmonary disease

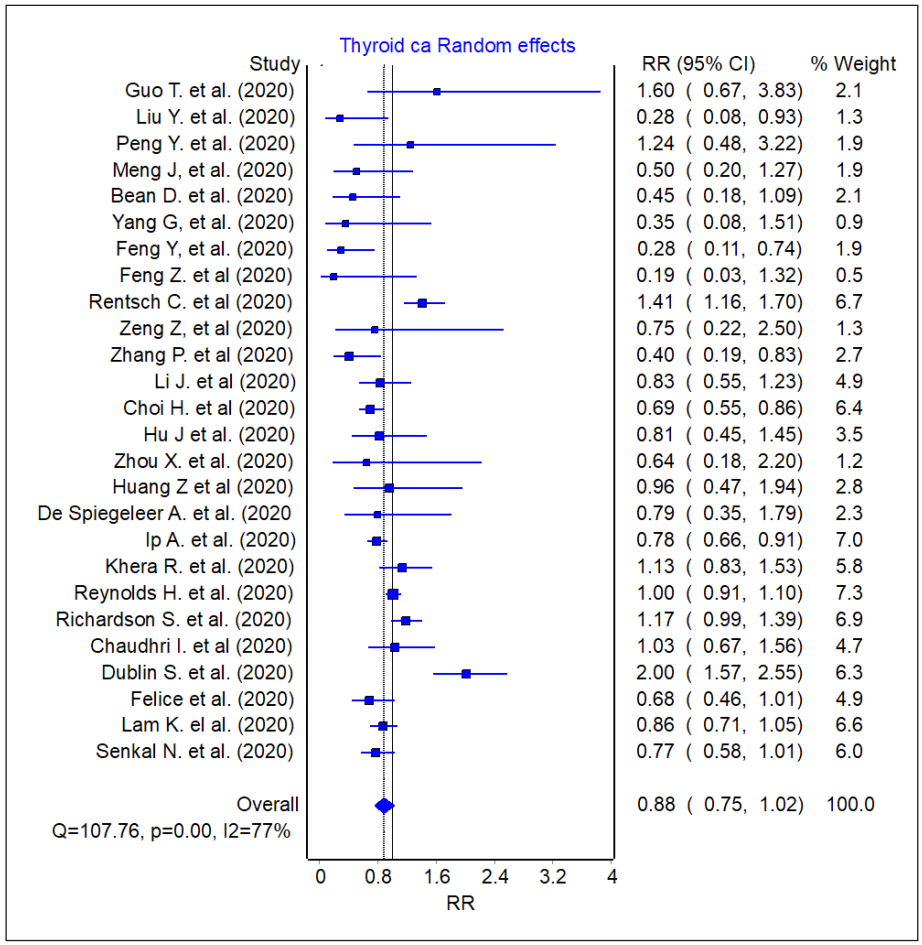

Figure 2. Forest plot of the meta-analysis of the association between angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) use and SARS-CoV-2 infection severity or mortality. Analysis model: random effect. OR — odds ratio; CI — confidence interval

Table 2. Association between the use of angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) and SARS-CoV-2 infection severity or mortality: summary of subgroup analyses

Subgroup	Studies (n)	Adjusted OR (95% CI)	p
Mean age (years)			
< 60	10	0.96 (0.71–1.30)	> 0.05
≥ 60	16	0.82 (0.67–1.0)	> 0.05
Male sex (%)			
< 55	18	0.84 (0.67–1.04)	> 0.05
≥ 55	8	0.88 (0.69–1.12)	> 0.05
Type of RAS inhibitors			
ARB	12	0.90 (0.76–1.06)	> 0.05
ACEI	11	0.90 (0.74–1.08)	> 0.05

RAS — renin–angiotensin system; OR — odds ratio; CI — confidence interval

ARB use did not increase the risk of severe disease or mortality from SARS-CoV-2 infection (OR = 0.88, 95% CI: 0.75–1.02, p > 0.05). Subgroup analyses were conducted to assess ACEI and ARB effects separately (Tab. 2) but no significant associations were found. Subgroup analyses were also negative for the effects of age (< 60 *vs*. 60+) or sex (Tab. 2).

Discussion

Our study found no evidence to support the hypothesis of increased SARS-CoV-2 risk with ACEI or ARB drugs. This would seem at odds with a previous finding that chronic use of ACEIs and ARBs was high among intensive care unit patients with non-COVID-19 sepsis [45]. However, it is possible that ACEIs/ARBs could be a marker of underlying comorbidities rather than being causal in SARS-CoV-2 severity or mortality.

Prior to the SARS-CoV-2 pandemic, Shinohara et al. published a meta-analytic study where they found a decreased risk of post-stroke pneumonia in patients treated with ACEIs compared to other antihypertensive drugs (RR: 0.61, 95% CI: 0.51–0.75; p < 0.001) [46]. In another meta-analysis, Liu et al. found that ARBs were associated with a decreased risk of pneumonia morbidity (OR = 0.55, 95% CI: 0.43–0.70, p < 0.01) and mortality (OR = 0.55, 95% CI: 0.44–0.69, p < 0.01) [19]. These findings could however be seen from the perspective that the prescription of ACEIs/ARBs may be a marker of good general medical care, given the well-evidenced preventative role of these medications in many cardiovascular and metabolic diseases.

The basis for the hypothesis of a probable ACEI/ARB-induced increase in ACE2 expression has been recently revised, evaluating the results of 12 animal and 11 human studies [47]. In animal studies, no significant changes in ACE2 expression were found, and in those where it was evidenced, it was when models of acute injury were used or at higher doses than those used in humans; furthermore, no increase in ACE2 expression induced by ACEIs/ARBs was evidenced in human studies [47].

It has been proposed that ARBs may have protective effects on severity and mortality in SARS-CoV-2 infection through increasing the production of angiotensin 1–7, reducing angiotensin II and contributing towards lung protection [48]. Recently, Liu et al. found that angiotensin II levels in the plasma of COVID-19 infected patients was markedly elevated and linearly associated to viral load and lung injury [49]. However, this may be a marker of general physiological stress during severe acute illness and not have specific drug-disease implications.

Our study is limited in that it only relies on observational studies and not RCTs and includes a relatively small number of participants. It would be important that future, more powered studies, re-evaluate the possible relevance of age (young *vs*. old), sex, and possible different roles of ACEI and ARB drugs. It would also be important to assess the risk of specific comorbidities (e.g. diabetes, hypertension, cerebrovascular disease, ischaemic heart disease) in the absence of ACEI/ARB drugs. For example, Feng et al. showed that hypertension without ACEI/ARB therapy was an independent risk factor for developing severe pneumonia irrespective of age [42].

In conclusion, the evidence available at present does not support the hypothesis of increased SARS-CoV-2 risk with ACEI or ARB drugs. However, more evidence needs to accumulate before this controversy can be resolved; in the meantime, clinicians may adopt a tailored, pragmatic approach that is supported by official recommendations [12, 50].

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Conflict of interest

None.

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Lack of association between angiotensin-converting enzyme (ACE) genotype and essential hypertension in Peruvian older people

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Abstract

Background: Epidemiological studies have shown an association between the ACE gene I/D polymorphism with arterial hypertension, specifically the DD genotype, in different populations. The objective of this study is to evaluate the association between ACE polymorphisms (Insertion, Deletion or I/D) and essential hypertension in a population of Lima, Peru.

Material and methods: This is a study of cases (essential arterial hypertension) and controls, with determination of the ACE I/D genotype.

Results: Cases (65) and controls (39) had a mean age (standard deviation) of 74.3 (7.9) and 72.6 (6.5) (p = 0.24). In cases, the genotype frequencies DD, ID, and II were 6 (9.2%), 28 (43.1%) and 31 (47.7%), respectively. In controls, the genotype frequencies DD, ID, and II were 6 (15.4%), 14 (35.9%) and 19 (48.7%). The Hardy-Weinberg equilibrium analysis in cases and controls was p = 0.93 and p = 0.23, respectively. No significant associations between genotype DD *vs.* ID + II (OR = 0.56, 95% CI: 0.17–1.87, p = 0.34) or II *vs.* DD + ID (OR = 0.95, 95% CI: 0.43–2.12, p = 0.92) and essential hypertension were found.

Conclusions: The ACE I/D polymorphism was not associated with hypertension in our sample.

Key words: hypertension; renin–angiotensin system; genetic polymorphism; angiotensin converting enzyme; Peru

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Introduction

Hypertension is one of the most common non-communicable diseases in the world, with a prevalence of 22% [1] and in Peru 23.7% [2]. Essential hypertension refers to primary hypertension where an aetiology has not been clearly identified. Arterial hypertension has been associated with various risk factors including age, sex, demographic, lifestyle, environmental and genetic. The heritability of hypertension ranges from 48 to 60% for systolic hypertension and 34 to 67% for systo-diastolic [3], although it should be noted that heritability does not identify which genetic difference is more significant or the mechanism by which it exerts its effect on blood pressure [3].

Currently, 2129 genes associated with hypertension have been reported, among which is the angiotensin-converting enzyme (ACE) gene [4]. The ACE enzyme converts inactive angiotensin I into active angiotensin II and also degrades bradykinin to maintain homeostasis of blood pressure. ACE is a membrane-bound dipepetidyl carboxypeptidase ectoenzyme, located in the endothelium of blood vessels and is the main component of the renin-angiotensin and kallikrein–kinin system. The ACE gene is encoded on the long arm of chromosome 17 (17q23), consists of 26 exons and 25 introns. The presence or absence of a 287bp element in the ACE gene gives rise to three genotypes: insertion (II), insertion/deletion (I/D) and deletion (DD). Epidemiological studies have shown an association between the ACE gene I/D polymorphism with arterial hypertension, specifically the DD genotype in different populations [5]. On the other hand, certain differences in response have been evidenced in the antihypertensive inhibitors of the angiotensin converting enzyme (ACEI) or angiotensin II receptor blockers (ARBs), according to ACE polymorphism and the study population [5].

The present study aims to evaluate the association between ECA polymorphisms (Insertion/Deletion or I/D) and hypertension essentially in a population of Lima, Peru.

Material and methods

An observational, retrospective case-control study was carried out. 104 patients (65 cases and 39 controls) equal to or older than 60 years were included. Patients with a diagnosis of essential hypertension verified in clinical history and receiving treatment with antihypertensives for more than 3 months were called cases; and controls were those with a clinical history and evaluation without criteria of arterial hypertension or taking antihypertensives. The study was conducted at the Hospital de Geriátrico of the Almenara Hospital in Lima, Peru, between January 2016 and December 2018. The 104 people of mestizo ancestry, from Lima, who entered the study, were part of an investigation on the use of angiotensin II antagonists, memory performance and its relationship with ACE polymorphisms. The research project was approved by the Almenara Hospital Ethics Committee, and all participants signed an informed consent. The method of patient selection was not probabilistic.

Genomic analysis

After signing the informed consent, whole blood samples were collected in EDTA tubes of each patient. The DNA was extracted from the leukocytes using the standard phenol/chloroform method and amplified by PCR (polymerase chain reaction). ACE I/D polymorphism (rs1799752) was detected using the method described by Franken et al [6].

Statistical analysis

Descriptive statistical data were presented as a percentage (%), mean with standard deviation (SD) and range. The Chi-square analysis was used for the Hardy-Weinberg equilibrium deviation evaluation. The genotype distribution and allele frequencies of each polymorphism were compared between cases and control subjects by the χ^2 test. In establishing the association between hypertension and ACE I/D genotypes, the odds ratio (OR) and 95% confidence intervals (CI) were used. It was considered statistically significant if $p < 0.05$. The SPSS statistical package was used to analyse the data.

Results

The population studied consisted of 46 men (44.2%) and 58 women (55.8%), with a mean age and standard deviation (SD) of 73.7 (7.4) years, range between 60–90 years. In the population studied the frequency of D/D, I/D and I/I genotypes was 12.65%, 43.66% and 43.66 respectively, with allelic D and I frequency of 34.5% and 65.5% respectively. The analysis of the distribution of genotype frequencies showed that it was consistent with a population in Hardy-Weinberg equilibrium ($\chi^2 = 0.1051$; $p = 0.746$) (Tab. 1).

The mean and standard deviation (SD) of age of the cases and controls were 74.34 (7.87) and 72.56 (6.60 years) ($p = 0.24$). The cases were male 32

Table 1. Characteristics of the population studied

Characteristics	Controls (n = 39)	Cases (n = 65)	p value
Age (± SD)	72.56 (6.60)	74.34 (7.87)	0.24
Sex			
Male (%)	14 (35.90%)	32 (49.23%)	0.19
Female (%)	25 (64.10%)	33 (50.77%)	0.19
Body mass index	27.28 (4.21)	28.02 (3.89)	0.37
Smoking	3 (7.69%)	2 (3.13%)	0.30
Dyslipidaemia	9 (23.08%)	27 (41.54%)	0.07
Diabetes mellitus type 2	7 (17.95%)	14 (21.54%)	0.66
Genotype			
D/D n (%)	6 (15.38%)	6 (9.23%)	0.42
I/D n (%)	14 (35.90%),	28 (43.08%)	0.47
I/I n (%)	19 (48.72%).	31 (47.69%)	0.92

SD — standard deviation

Table 2. Relationship between angiotensin convertase enzyme (ACE) polymorphisms and essential hypertension in a population of Lima, Peru

Genotype ACE	Controls (n = 39)	Cases (n = 65)	OR	95% CI	p value
DD *vs.* ID + II n (%)	6 (15.38)	6 (9.23%)	0.56	0.17–1.87	0.34
ID *vs.* II + DD n (%)	14 (35.9%)	28 (43.08)	1.35	0.60–3.06	0.47
II *vs.* DD + ID n (%)	19 (48.72)	31 (47.9%)	0.95	0.43–2.12	0.92
D *vs.* I n (%)	26 (33)	40 (31%)	0.89	0.49–1.62	0.70
The Hardy-Weinberg equilibrium (p value)	0.23	0.93			

OR — odds ratio; CI — confidence interval

(49%) and female 33 (51%), while controls were male 14 (36%) and female 25 (64%). In the cases the genotype frequency DD, ID, and II were 6 (9.23%), 28 (43.08%), 31 (47.69%) respectively. In the controls the genotype frequency DD, ID, and II were 6 (15.38%), 14 (35.90%), 19 (48.72%). The Hardy-Weinberg equilibrium analysis in cases and controls was p = 0.93 and p = 0.23 respectively. No significant association of genotype DD *vs.* ID + II (OR = 0.56, 95% CI: 0.17–1.87, p = 0.34) or II *vs.* DD + ID (OR = 0.95, 95% CI: 0.43–2.12, p = 0.92) with essential hypertension was found (Tab. 2).

Discussion

The present study did not find an association between ACE polymorphisms and essential hypertension in a population of Lima, Peru.

The results of studies on the relationship between ECA polymorphisms and essential hypertension differ significantly depending on the geographic location and population studied. The main study with positive results is the meta-analysis conducted by Mengesha et al. in the African continent, which included 6 studies, finding that patients with the D allele were 1.49 times more likely to develop essential hypertension compared to the carriers of the I allele (OR: 1.49; CI: 1.07–2.07), additionally found that those from sub-Saharan Africa were more susceptible than those from North Africa [5]. A study conducted in the USA with Mexican-Americans found an association between the D allele and essential arterial hypertension [7]. Studies in India have also reported an association between the ACE/(D/D) genotype and essential hypertension [8–11].

On the other hand, the negative results are reported by Agerholm et al. [12], the meta-analytical

study included 45 studies in white people in Europe and the US, finding no relationship between the ACE gene and essential hypertension. In addition, two studies have been published with the same negative results between Hawaiian Americans and African Americans [13, 14].

In Latin America, a study in Colombia (Bucaramanga) found that DD genotype was 1.56 times more frequent in hypertensive patients, compared to allele I [15]. Bonfim-Silva et al. [16] in their study with Afro-Brazilian and Caucasian population found no association; neither did the study conducted in Cuba in a multi-ethnic sample [17]. A recent study in Brazil also found no relationship; however, this relationship became significant only when ACE and ACE2 polymorphisms were combined [18]. Prior to this study, the only study conducted in Peru (Lima and Chincha), was that of Lizaraso et al. and found no relationship between these polymorphisms and essential hypertension [9].

The importance of knowing the association of ACE gene and essential hypertension is to know if there is a genetic basis in the effectiveness of antihypertensive pharmacotherapy with angiotensin converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs). It has been described that the effectiveness of ACEIs is diminished in the African and African-American population and these antihypertensives are not of first choice in that population [20, 21]. Coincidentally the ACE D/D genotype is related to essential hypertension in this population [5]. It has been described that the rate of early responses to ramipril is more frequent in patients with genotypes ID and II, compared to DD, in patients from India; once again it is compatible with the finding of the association of DD with HT in that country [22]. Another study in Malaysia, found that DD carriers respond better to enalapril or lisinopril than ID and II [23]. On the other hand, genotypes II respond better than DD or ID to ARB such as ibersartan [24]. One of the practical objectives of this type of pharmacogenetic studies is to convert the ACE polymorphism determination into a marker of individualized antihypertensive response to ACEIs and ARBs.

The present study has some limitations. The main one is the number of patients is relatively small. However, it provided genetic data that can be used to initiate other studies designed to know the pharmacogenetics of ACEIs and ARBs in the Peruvian population, having ACE genotypes as markers.

In conclusion, the present study did not find an association between ACE polymorphisms (Insertion/Deletion or I/D) and essential hypertension in the study population. More research is required in different populations of the country, adding other candidate genes.

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Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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Serum amphiregulin and cerebellin 1 levels in primary hypertension patients

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Abstract

Background: Hypertension is a major risk factor for cardiovascular diseases, stroke, congestive heart disease and renal failure. Primary hypertension is a multi-factorial complex disease and its exact etiology still remains unknown. In this study we aimed to compare serum amphiregulin and cerebellin-1 levels of primary hypertension patients with healthy subjects.

Material and methods: Forty-four hypertensive patients and 44 healthy people were included. Patients with systolic blood pressure measurements ≥ 140 mm Hg and diastolic blood pressure measurements ≥ 90 mm Hg were evaluated as hypertensive. Serum amphiregulin and cerebellin 1 levels were measured using ELISA method.

Results: Mean amphiregulin level was 32.1 (10.2–72.5) pg/mL in hypertension group and 36.9 (15.9–109.5) pg/mL in control group (p = 0.002). Mean cerebellin 1 levels were comparable in both groups, 82.1 (23.9–286.1) pg/mL in hypertensive group and 95.1 (60.2–293) pg/mL in control group (p = 0.261). Serum amphiregulin to predict hypertension was found to be ≤ 23 pg/mL with specificity of 97% and sensitivity of 48.5% (AUC = 0.74; 95% CI, 0.62–0.86; p = 0.001).

Conclusions: Hypertension is associated with lower serum amphiregulin concentrations.

Key words: amphiregulin; cerebellin 1; primary hypertension; ELISA

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Introduction

Hypertension is a major risk factor for cardiovascular diseases, stroke, congestive heart disease and renal failure [1]. Primary hypertension affecting approximately 95% of all cases is a multifactorial complex disease and its exact etiology still remains unknown. Genetic and environmental stimuli and their interactions are thought to determine the disease [2]. It is estimated that over 1 billion people have been affected by primary hypertension [3]. Up to 54% of stroke and 47% of ischemic heart disease may be attributed to high blood pressure worldwide [1].

Amphiregulin is a protein which acts as a ligand for epidermal growth factor (EGF) [4]. Epidermal growth factor is detectable in the serum of healthy individuals, as well as many other organs including: placenta, ovaries, testes, heart, pancreas, spleen, bone marrow, kidneys, lungs, colon and breasts [4, 5]. It has been shown that EGF can play a role in blood pressure regulation and deteriorate endothelial function [6, 7].

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Cerebellin is derived from precerebellin and has neuromodulatory functions such as maintaining of synaptic structures and modulating of their functions in the brain [8]. It has been determined that cerebellin is secreted from adrenal glands, neuroendocrine system and pancreas [9–12]. Cerebellin has a stimulating effect on the secretion of aldosterone, cortisol and catecholamine from the adrenal glands and this may contribute to an increase in blood pressure [13].

To the best of our knowledge the interplay between cerebellin, amphiregulin in primary hypertension was scarcely investigated.

Material and methods

The study followed the tenets of the Declaration of Helsinki and was approved by the institutional ethics committee (approval number: 2017/20/18) and informed consent was obtained from all of the participants. 102 patients who were admitted to the Emergency Department of Kahramanmaraş Sütçü İmam University Faculty of Medicine between January 2019 and December 2019 with headache and elevated arterial blood pressure older than 18 years of age were included in the study. Physical examination and arterial pressure measurements of these patients were performed. Arterial blood pressure was measured using a suitable cuff after resting the patients in a physically available quiet room for 5 minutes. A special attention was paid to that the patients did not drink cigarettes, tea, coffee or eat in the last 30 minutes. The average of two or more office measurements obtained on two or more occasions of 140/90 mm Hg and above was defined as hypertension [14–16]. Patients with cerebrovascular event, previously diagnosed hypertension patients, antihypertensive drug users were excluded. Patients who were obese or diagnosed with diabetes, Cushing syndrome, rheumatologic disease, chronic headache, migraine, intracranial mass, acute and chronic renal failure and active infection were also excluded from the study. After applying the exclusion criteria listed above, 55 of 102 patients were referred to the cardiologist for further evaluation. Secondary hypertension (renal parenchymal disease, renovascular disease, primary aldosteronism, hyperthyroidism, hypothyroidism, hyperparathyroidism, pheochromocytoma, coarctation of the aorta, drug-induced hypertension and etc.) and white coat hypertension were ruled out. Echocardiographic evaluation was performed in all hypertensive patients. End-organ damage was investigated and routine laboratory values of the patients were examined. Finally forty-four newly diagnosed hypertension patients without end-organ damage were included in the study (Fig. 1). As the control group, 44 healthy volunteers with similar age and sex who presented to the outpatient clinic were

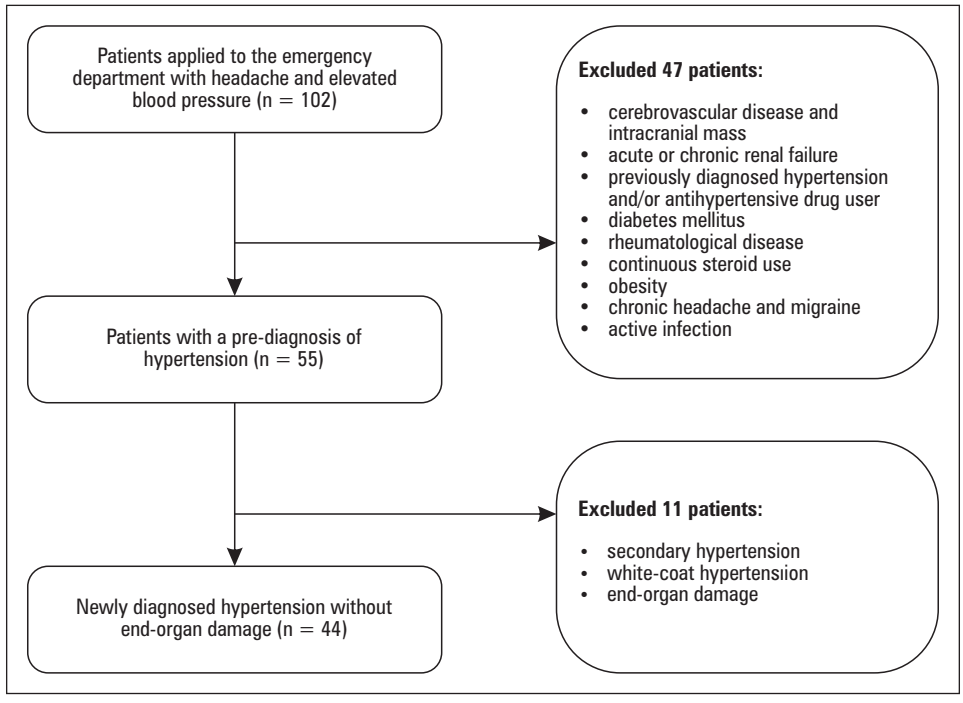

Figure 1. Flow chart shows the patient selection process

included in the study. Blood samples were collected and centrifuged at 4000 g for 10 minutes. The serum samples were collected and stored at –80°C until required for analysis.

Transthoracic echocardiographic examinations were performed by experienced echocardiographers who were blinded about the clinical information of the subjects via the Vivid 7® cardiac ultrasonography system (GE Ving-Med Ultrasound AS; Horten, Norway) with 2.5- to 5-MHz probes. The supine and left lateral positions were conducted for each patient with 2D, M-mode, pulsed and color flow Doppler echocardiography. Single lead electrocardiogram continuously recorded. For all measurements, the average of at least three cardiac cycles was evaluated. For the conventional Doppler echocardiographic examinations and M-mode measurements, the European Society of Echocardiography guideline criteria were used [17].

Enzyme-linked immunosorbent assay (ELISA)

Serum amphiregulin (Human Amphiregulin ELISA kit catalog number: 201-12-3148 Shanghai Sunred Biological Technology, Shanghai, China) and cerebellin 1 (Human Cerebellin1 ELISA kit; catalog number: 201-12-3438 Shanghai Sunred Biological Technology, Shanghai, China) levels were measured using enzyme-linked immunosorbent assay method according to the manufacturer's protocol. Specimen absorbance values were determined on Multiskan FC microplate reader (Thermo Fisher Scientific) at a wavelength of 450 nm. Values were expressed as picogram/mL. The intra-assay coefficient of variance (CV), inter-assay CV, detection range and sensitivity of the amphiregulin kit were reported as < 10%, < 12%, and 4–1000 pg/mL and 3.747 pg/mL, respectively. The intra-assay CV, inter-assay CV, detection range and sensitivity of the cerebellin-1 kit were reported as < 11%, < 12%, and 5–1500 pg/mL and 4.385 pg/mL, respectively.

Statistical analysis

Data management and analysis were performed using the SPSS program version 14 (SPSS Inc., Chicago, IL) and a two-sided p-value ≤ 0.05 was considered statistically significant. Continuous data were expressed as mean ± standard deviation or median, and categorical data as percentages. Means were compared via an independent sample t test, and if there was no normal distribution, via a Mann-Whitney U test with median. Categorical data were evaluated using the chi square test as appropriate. The relationships between variables were assessed with Pearson correlation coefficient for normally distributed variables and by Spearman's rank correlation coefficient for non-normally distributed variables. A receiver operator characteristic (ROC) curve analysis was performed to identify the optimal cut-off point of serum amphiregulin and levels for the prediction of hypertension. MedCalc (v. 12.7.8) was used to perform ROC curve analysis. The area under the curve (AUC) with 95% confidence interval was calculated. The optimal cut-off value of serum amphiregulin level was defined as the value associated with the highest sum of sensitivity and specificity-1. We used univariate analysis to quantify the association of variables with hypertension. The variables found to be statistically significant in the univariate analysis and other potential confounders were used in multivariate logistic regression model with backward stepwise method in order to determine the independent prognostic factors of hypertension

Results

Clinical, laboratory and echocardiographic data of two groups were shown in Table 1. There was no significant difference between groups regarding age and sex. Systolic pressure in hypertensive group was 165 ± 5 mm Hg and in control group was 117 ± 12 mm Hg ($p < 0.001$). Diastolic pressure in hypertensive group was 98 ± 7 mm Hg and in control group was 77 ± 6 mm Hg ($p < 0.001$). There were significant differences between the two groups in terms of amphiregulin, blood urea nitrogen (BUN) and potassium levels. Mean amphiregulin level was 32.1 (10.2–72.5) pg/mL in hypertension group and 36.9 (15.9–109.5) pg/mL in control group. Amphiregulin level was significantly lower in hypertensive group ($p = 0.002$). Mean cerebellin 1 levels were 82.1 (23.9–286.1) pg/mL in hypertensive group and 95.1 (60.2–293) pg/mL in control group. Cerebellin 1 levels were similar in hypertension and control groups ($p = 0.26$). There was not any correlation between systolic pressure, diastolic pressure and serum amphiregulin levels in hypertensive patients. Serum amphiregulin was correlated only with serum creatinine levels ($r = 0.25$, $p = 0.03$). Serum BUN levels were 26.8 ± 8.2 pg/mL in hypertension group and 16.4 ± 4.8 pg/mL in control group ($p = 0.001$). Serum potassium level was 4.6 ± 0.4 mg/dL in hypertension group and 4.3 ± 0.2 mg/dL in control group ($p = 0.001$). Standard echocardiographic and other laboratory parameters were similar between two groups.

Optimal cut-off levels of serum amphiregulin to predict hypertension was found to be ≤ 23 pg/mL with specificity of 97% and sensitivity of 48.5%

Table 1. Baseline characteristics of study patients

Parameter	Hypertensive	Control	p value
Baseline characteristics			
Age [y]	49.4 ± 11	48 ± 10	0.622
Male/female, n	21/23	22/24	0.831
SBP [mm Hg] (mean ± SD)	165 ± 5	117 ± 12	< 0.001
DBP [mm Hg] (mean ± SD)	98 ± 7	77 ± 6	< 0.001
Laboratory findings			
Sodium [mg/dL] (mean ± SD)	141.5 ± 3.8	140.5 ± 3.0	0.158
Potassium [mg/dL] (mean ± SD)	4.6 ± 0.4	4.3 ± 0.2	0.001
Creatinine [mg/dL] (mean ± SD)	0.7 ± 0.2	0.7 ± 0.1	0.101
BUN [mg/dL] (mean ± SD)	26.8 ± 8.2	16.4 ± 4.8	< 0.001
Chloride [mg/dL] (mean ± SD)	103 ± 5	102 ± 4	0.308
Calcium [mg/dL] (mean ± SD)	9.67 ± 0.5	10 ± 0.1	0.495
AST [U/L] (mean ± SD)	21 ± 6.1	23.7 ± 8	0.085
ALT [U/L] (mean ± SD)	20 ± 9	22 ± 11	0.318
Blood glucose [mg/dL] (mean ± SD)	102 ± 23	97 ± 13	0.359
MPV [fL] (mean ± SD)	10.4 ± 0.8	9.9 ± 1.7	0.173
Plt [10^3/mm^3] (mean ± SD)	262 ± 70	240 ± 63	0.162
Hb [g/dL] (mean ± SD)	14.2 ± 1.7	13.8 ± 1.8	0.392
HCT (%) (mean ± SD)	41.1 ± 4.5	42.4 ± 4.3	0.212
WBC [10^3 mm^3] (mean ± SD)	8.0 ± 1.7	8.3 ± 2.4	0.325
RBC [10^6 U/L] (mean ± SD)	5.0 ± 0.6	4.9 ± 0.3	0.452
Amphiregulin [pg/mL] [median (IQR)]	32.1 (10.2-72.5)	36.9 (15.9-109.4)	0.002
Cerebellin [pg/mL] [median (IQR)]	82.1 (23.9-286.1)	95.1 (60.2-293)	0.261
Echocardiographic findings			
Mitral E velocity [cm/s] (mean ± SD)	87.5 ± 9.3	91 ± 14.4	0.175
Mitral A velocity [cm/s] (mean ± SD)	62.4 ± 10.5	66 ± 14.5	0.185
E/A ratio	1.4 ± 0.2	1.5 ± 0.2	0.489

→

Table 1. Baseline characteristics of study patients

Parameter	Hypertensive	Control	p value
DT [ms] (mean ± SD)	187.7 ± 9.8	188 ± 12.7	0.689
IVRT [ms] (mean ± SD)	87.6 ± 3	84.4 ± 14	0.107
LVEF (%) (mean ± SD)	66 ± 5	68 ± 5	0.071
Septum thickness [mm] (mean ± SD)	9.6 ± 1.2	9.2 ± 1.10	0.146
Posterior wall thickness [mm] (mean ± SD)	8.8 ± 3.4	8.0 ± 1	0.133
Left atrial diameter [cm] (mean ± SD)	34 ± 3.6	34 ± 2.2	0.88

SBP — systolic blood pressure; DBP — diastolic blood pressure; BUN — blood urea nitrogen; AST — aspartate aminotransferase; ALT — alanine aminotransferase; MPV — mean platelet volume; PLT — platelet; Hb — hemoglobin; HCT — hematocrit; WBC — white blood cell; RBC — red blood cell; DT — deceleration time; IVRT — isovolumetric relaxation time; LVEF — left ventricle ejection fraction; SD — standard deviation; IQR — interquartile range

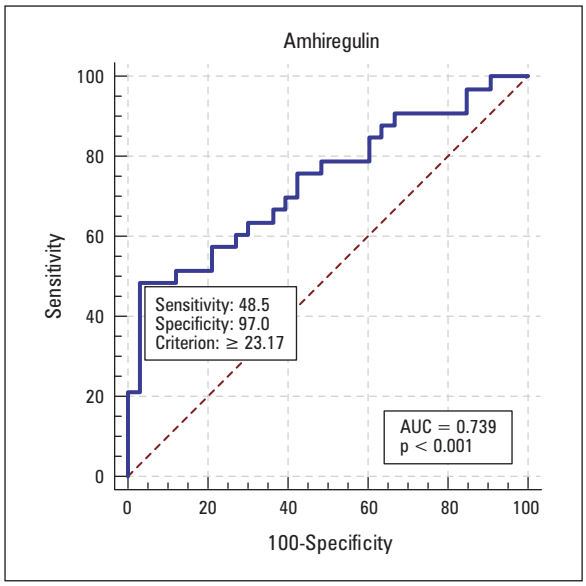

Figure 2. Receiver operating characteristic (ROC) curve analysis of amphiregulin to predict hypertension

[AUC = 0.74; 95% confidence interval (CI): 0.62–0.86; p = 0.001] (Fig. 2).

In the multiple logistic regression model, serum amphiregulin levels [odd ratio (OR) = 1.04, 95% CI: 1.01–1.18, p = 0.02] and BUN (OR = 1.10, 95% CI: 1.02–1.18, p = 0.01) were associated with hypertension after adjusting for the confounding variables, which were either found to be statistically significant in the univariate analysis and for the variables correlated with serum amphiregulin levels (Tab. 2).

Discussion

To the best of our knowledge, this study is the first to investigate amphiregulin and cerebellin 1 in hypertensive patients. It was revealed in this study that amphiregulin levels were low in newly diagnosed hypertension patients and low amphiregulin level was an independent predictor of newly diagnosed

Table 2. Univariate and multivariate analyses for predicting hypertension

Variable	Univariate		Multivariate	
	p	OR (95% CI)	p	OR (95% CI)
Amphiregulin	0.005	1.047 (1.014–1.081)	0.022	1.042 (1.006–1.079)
BUN	< 0.001	1.121 (1.055–1.190)	0.014	1.095 (1.018–1.178)
Potassium	0.057	3.076 (0.969–9.769)		
Variables which correlated with amphiregulin				
Creatinine	0.099	7.827 (0.679–90.217)		

All the variables from Table 1 were examined and only those significant at p < 0.05 level and correlated with amphiregulin are shown in univariate analysis. Multivariate logistic regression analysis including all the variables in univariate analysis with enter method. CI — confidence interval; OR — odds ratio; BUN — blood urea nitrogen

hypertension. It was found that cerebellin levels did not differ between the healthy group and the newly diagnosed hypertensive group. We also showed that serum urea level is high in hypertensive group and urea levels are associated with hypertension de novo.

Many studies have shown that EGF is associated with vascular diseases such as atherosclerosis and hypertension through epidermal growth factor receptor (EGFR). The EGFR is expressed in vascular smooth muscle cells, endothelial cells, macrophages and regulatory T lymphocytes, and all of these cells also secrete EGFR ligands [5]. Preventive effect of EGFR on excessive hypertrophic growth of cardiomyocytes and contribution of EGFR to the appropriate vascular wall architecture and vessel reactivity have been shown. With these effects EGF has roles supporting a physiological vascular tone and is also required for physiological cardiovascular tissue homeostasis [18]. Transactivation of EGF/ /EGFR reported to cause vasoconstriction [19]. In human studies plasma EGF levels were found to be correlated with diastolic blood pressure and carotid artery stiffness [20]. In an experimental study, an EGFR inhibitor, erlotinib failed to reduce elevated blood pressure in angiotensin II infused mice but protected animals from perivascular fibrosis [21]. Epidermal growth factor and its receptor are widely expressed in kidney and modulate glomerular hemodynamics and renal metabolism. Epidermal growth factor and its signaling involve in cell growth, proliferation, and renal electrolyte homeostasis. Activation of EGFR plays role in renal hemodynamics and electrolyte metabolism in kidney under physiological conditions [22]. Epidermal growth factor induces constriction of both preglomerular and postglomerular arterioles and reduces glomerular filtration and perfusion that may cause hypertensive effect. On the other hand, intravenous infusion of EGF for several days decreased the epithelial sodium channel activity, prevented the development of hypertension and attenuated renal glomerular and tubular damage in an experimental study [23]. Epidermal growth factor and EGF ligands such as amphiregulin are expected to be high in hypertensive patients. Contrary to our expectations serum amphiregulin levels were lower in hypertensive patients than controls in our study. When analyzed with the data in the literature, amphiregulin may have complex roles in the pathogenesis of hypertension. Amphiregulin may cause different effects in pathological and physiological processes as EGF and EGFR discussed in the above articles. Rather than activator roles amphiregulin may have regulatory functions in blood pressure. The patients in our study group were hypertensive and were not taking any antihypertensive drugs. Amphiregulin levels in these patients may have been found to be low in order to reduce vasoconstriction in vascular smooth muscle due to the body's compensation mechanisms. On the other hand, the vasoconstrictor effects of amphiregulin on glomerular precapillary and post-capillary arterioles may have been tried to be compensated by reducing the release of amphiregulin in hypertensive patients. Perhaps the primary cause of the hypertension in these patients may be due to a mutation in the amphiregulin gene or the amount of amphiregulin may not be released enough to balance the vascular tone. More comprehensive and large-scale studies are needed to clarify the exact mechanism.

The early stage of primary hypertensive kidney involvement is characterized by afferent arteriolar vasoconstriction. Thus, renal blood flow and effective renal plasma flow (ERPF) are reduced, glomerular filtration rate (GFR) is maintained within relatively normal limits and filtration fraction (GFR/ERPF) increases [24, 25]. Microproteinuria occurs due to the increase in the filtration fraction. Microproteinuria is responsible for the onset and progression of tubulointerstitial injury [24, 26]. A decrease in renal blood flow reduces tubular urea secretion. Excessive absorption of sodium and water from the proximal tubules increases post-secretory urea absorption. Therefore, an increase in serum urea level may occur [27]. Since these hemodynamic events are potentially reversible, it is very important to detect kidney involvement at an early stage. We revealed in this study that the blood urea levels of newly diagnosed hypertension patients were high. In addition, high blood urea values were an independent variable for hypertension. Because blood urea levels are affected by many pathologies, it may not be appropriate to use this parameter in the first diagnosis of primary hypertension.

Investigations about the effects of cerebellin on circulation are very limited. Rucinski et al. demonstrated that cerebellin-derived peptides have adrenocorticotropic hormone (ACTH)-like effects on corticosterone output and proliferative activity of cultured rat adrenocortical cells [28]. Previous studies showed that cerebellin is a potent stimulator of direct norepinephrine release by rat adrenal medulla and enhances adrenocortical steroid secretion. Adrenocortical secretagogue effect of cerebellin is mediated by locally released catecholamines that act on the cortex in a paracrine manner [29, 30]. Gauli et al. reported that autonomous aldosterone secretion is more prevalent among patients with primary hypertension and significantly correlated with systolic

and diastolic arterial blood pressure [31]. Cerebellin increases norepinephrine release from the adrenal medulla. Previous studies have shown a relationship between hypertension and sympathetic system activation. Before starting the study we hypothesized that the increase of sympathetic activity in hypertensive patients may be caused by high cerebellin levels. However, cerebellin-1 levels were lower in hypertensive patients than in the control group, without statistical significance.

In another study, we compared the serum amphiregulin and cerebellin 1 levels of severe preeclampsia patients with healthy pregnant women and healthy normotensive nonpregnant women control subjects. We found significantly decreased serum amphiregulin and cerebellin 1 levels in severe preeclampsia patients compared with healthy pregnant women and controls [32]. Serum amphiregulin was also lower in patients with hypertension in current study. Serum cerebellin levels were similar in hypertensive and healthy individuals, contrary to our expectations. As it is known, compared to primary hypertension, preeclampsia is a more acute and rapidly progressing pathology. Hypothetically rapid and appropriate cerebellin secretion response may not occur in preeclampsia patients compared to those of primary hypertension patients.

Our study has some limitations. If we studied aforementioned molecules such as norepinephrine and aldosterone that contributes to the pathogenesis of hypertension in combination with amphiregulin and cerebellin 1, we would have achieved more precise results. According to the results of our study, serum amphiregulin indicate the presence of hypertension rather than its severity.

In conclusion, serum amphiregulin appears to be lower in primary hypertension patients when compared to normotensives. Low amphiregulin (≤ 23 pg/mL) can be used to support the diagnosis of primary hypertension.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Utility of Systematic Coronary Risk Evaluation (SCORE) system to predict coronary artery disease severity in low to moderate risk hypertensive patients undergoing elective coronary angiography

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Abstract

Background: Coronary artery disease (CAD) is the leading cause of mortality in hypertensive patients. Systematic Coronary Risk Evaluation (SCORE) is the preferred scoring system to predict future fatal cardiovascular events in hypertensive patients. However, the relationship between SCORE and coronary atherosclerosis is not well described. We aimed to investigate whether SCORE has a relationship with CAD severity in hypertensive patients, even in the absence of high risk features.

Material and methods: Four hundred and fifty-two hypertensive patients who underwent elective coronary angiography and defined as low or moderate risk according to SCORE were included into the study. Patients were divided into two groups. Patients with a SCORE < 1% were defined as low risk group, and patients with a SCORE ≥ 1% and < 5% were defined as moderate risk group. The groups were compared regarding CAD severity.

Results: The frequency of stenotic CAD and multivessel disease, and mean SYNTAX score, were significantly higher in SCORE ≥ 1%, and < 5% group compared to patients with SCORE < 1%. Correlation analysis revealed a significant positive moderate correlation between SCORE and SYNTAX score (Pearson's r: 0.679, $p < 0.001$). ROC curve analysis demonstrated that a SCORE ≥ 3% predicted SYNTAX score > 22 with a sensitivity of 75% and a specificity of 86.5% (AUC: 0.879, $p < 0.001$). Furthermore, multivariate analysis demonstrated that SCORE was an independent predictor of stenotic CAD (OR: 1.616, $p < 0.001$), multivessel disease (OR: 1.913, $p < 0.001$), and SYNTAX score > 22. (OR: 1.817, $p < 0.001$).

Conclusion: Our results suggest that SCORE is associated with CAD severity in hypertensive patients even in the absence of high risk features. The SCORE system may be useful in further risk stratification of hypertensive patients with moderate risk features and suspected CAD.

Key words: hypertension; coronary artery disease; coronary angiography; SCORE; SYNTAX score

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Introduction

Hypertension is an important risk factor for both structural and functional damage in cardiovascular system that leads a significant increase in morbidity and mortality [1, 2]. Atherosclerosis is the main manifestation of hypertension-related vascular injury, and coronary artery disease (CAD) is the most dangerous consequence of hypertensive end-organ damage and is the leading cause of mortality in hypertensive patients [3, 4]. Hereby, risk stratification of hypertensive patients remains the cornerstone of the adequately prevention of future cardiovascular events. Systematic Coronary Risk Evaluation (SCORE) system is a validated scoring system that predicts the 10-year risk of a first fatal atherosclerotic cardiovascular event, in relation to age, gender, smoking, total cholesterol, and systolic blood pressure (SBP) [5]. European guidelines strongly recommend to use SCORE system for cardiovascular risk assessment of hypertensive patients except those who are at high or very high risk due to known cardiovascular disease (CVD) or associated conditions [4, 6]. However, SCORE only predicts the 10-year risk of a first fatal atherosclerotic cardiovascular event, and its association with CAD and CAD severity in low and moderate risk hypertensive patients remains unclear. Since the CAD is the leading cause of the death in hypertensive patients, definition of association of SCORE with CAD severity may provide useful information for further risk assessment in clinical practice, in particular, in hypertensive patients with low and moderate risk.

SYNTAX score is an angiographic tool that is calculated based on anatomical location and potential functional importance of coronary lesions and is used to estimate the extend, complexity and severity of CAD [7]. SYNTAX score is the cornerstone of the classification of CAD severity and is an important prognostic factor in patients with CAD [8]. Therefore, in the present study, the association of SCORE system with CAD severity in hypertensive patients who don't have high risk features was investigated. We mainly aimed to investigate whether SCORE has a relationship with SYNTAX score in hypertensive patients classified as being at low and moderate risk according to SCORE system and undergoing elective coronary angiography.

Material and methods

Study design

A total of 525 consecutive hypertensive patients who were between the age 40 and 65 and at low or moderate risk according to SCORE system, and underwent elective diagnostic coronary angiography from January 2015 to November 2019 were enrolled. Among these patients, 73 patients (patients with left ventricular hypertrophy (LVH), microalbuminuria, and retinopathy) were excluded due to presence of asymptomatic hypertension-mediated organ damage that increases the cardiovascular risk independently. As a consequence, the remaining 452 hypertensive patients were included into the study. Since the SCORE system is validated for the subjects between the age 40 and 65, patients younger than 40 years and older than 65 years were not screened for the study. Patients with established CVD or its equivalent or at high (SCORE ≥ 5% and < 10%) or very high (SCORE ≥ 10%) risk were also excluded at baseline and were not screened for the study.

Hypertension was defined as SBP ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg in repeated measurements, and/or known treatment with antihypertensive medications. Active smoking was defined as the current regular use of cigarettes. All patients were evaluated with a detailed anamnesis, cardiac and systemic physical examination, electrocardiography and echocardiography. Laboratory analyses were performed from venous blood samples obtained after an overnight fasting. The study was conducted in full accordance with the Declaration of Helsinki and approved by the local ethics committee.

Systematic Coronary Risk Evaluation (SCORE)

SCORE is the preferred scoring system to estimate the 10-year risk of a first fatal atherosclerotic cardiovascular event, in relation to age, gender, smoking, total cholesterol, and SBP. Cardiovascular risk assessment with the SCORE system is strongly recommended for all hypertensive patients who are not already at high or very high risk due to manifest overt CVD or chronic kidney disease, or diabetes mellitus, or a markedly elevated single risk factor or LVH [4, 5]. Cardiovascular risk is analyzed in four groups based on SCORE. A calculated SCORE ≥ 10% indicates patients at very high risk, a SCORE ≥ 5% and ≤ 10% indicates patients at high risk, a SCORE ≥ 1% and < 5% indicates patients at moderate risk, and a SCORE < 1% indicates patients at low risk [4–6]. SCORE can be easily calculated from "SCORE charts" for men and women, separately. There are two suggested SCORE charts for low risk and high risk countries, respectively. Since the study conducted in Turkey, we used the "SCORE — European High

Risk Chart" for calculation of SCORE [6]. In the present study, we divided the study population into two groups according to SCORE system. Patients with a calculated SCORE < 1% were assigned to the low risk, and patients with SCORE ≥ 1% and < 5% were assigned to the moderate risk group.

Coronary angiography and SYNTAX score

All patients underwent coronary angiography in elective conditions due to positive or suspected result of non-invasive tests. The classification of CAD was made based on coronary angiography results. Presence of ≥ 50% obstruction in any coronary artery was defined as stenotic CAD. Number of stenotic vessels and SYNTAX score were used to estimate the extend and severity of CAD. The presence of CAD was categorized as stenotic CAD (one vessel), or multivessel disease (MVD) according to the number of vessel with ≥ 50% stenosis.

SYNTAX score is calculated for the vessels with a diameter > 1.5 mm and with a stenosis ≥ 50%, and estimates the extend, complexity and severity of CAD using various anatomical and functional parameters [7, 8]. Also, SYNTAX score is a predictor of adverse events in patients with CAD, and while a SYNTAX score ≤ 22 indicates low risk patients for cardiovascular events, a SYNTAX score > 22 defines the intermediate to high risk patients [8, 9]. Therefore, in the present study, SYNTAX score was calculated for all vessels > 1.5 mm diameter and with a stenosis ≥ 50%, according to SYNTAX score calculator (www.syntaxscore.com). All digital coronary angiograms were evaluated by two independent experienced cardiologists. In case of disagreement, the final decision was achieved by consensus.

Statistical analysis

Continuous and categorical variables were expressed as mean ± standard deviation and percentages, respectively. The categorical variables were compared with the chi-square test or Fisher's exact test. The normality distribution of continuous variables was tested with Kolmogorov-Smirnov test. Continuous variables between the two groups were compared with Student's t test. Correlation between SCORE and SYNTAX score was assessed with Pearson's correlation coefficient. Receiver operating characteristics (ROC) curve analysis was performed to determine the area under the curve, and cutoff value of SCORE for predicting SYNTAX score >22. Multivariate logistic regression analysis was performed to define the independent predictors of stenotic CAD, MVD and SYNTAX score > 22. A p-value of < 0.05 was considered to indicate statistical significance.

Results

Among study population, 171 patients had a SCORE < 1%, and 281 patients had a SCORE ≥ 1%, and < 5%. Due to the nature of the SCORE system, the frequency of women (80.7%) were higher in patients with SCORE < 1% whereas, the frequency of men (68%) were higher in the SCORE ≥ 1% and < 5% patient groups. In the same sense, patients with SCORE ≥ 1%, and < 5% were older and had higher blood pressure levels compared to patients with SCORE < 1%. Also, dyslipidemia was more frequent in SCORE ≥ 1%, and < 5% group. Importantly, the frequency of stenotic CAD and multivessel disease, and mean SYNTAX score, were significantly higher in SCORE ≥ 1%, and < 5% group compared to patients with SCORE < 1%. Table 1 demonstrates the clinical, laboratory, and angiographic characteristics of patients according to SCORE system. When comparing the patients according to SYNTAX score, patients with SYNTAX score > 22 were older, and had higher blood pressure levels compared to patients with SYNTAX score ≤ 22. Moreover, the mean SCORE was significantly higher in the group of patients with SYNTAX score > 22 compared to patients with SYNTAX score ≤ 22 (3.48 ± 1.26 *vs.* 1.75 ± 1.38, p < 0.001). Table 2 shows the characteristics of patients according to SYNTAX score. Correlation analysis revealed a significant positive moderate correlation between SCORE and SYNTAX score (Pearson's r: 0.679, p < 0.001). Also, ROC curve analysis demonstrated that a SCORE ≥ 3% predicted SYNTAX score > 22 with a sensitivity 75% and a specificity 86.5% [area under the curve (AUC): 0.879, p < 0.001] (Fig. 1)

Furthermore, multivariate logistic regression analysis demonstrated that SCORE was an independent predictor of stenotic CAD [odds ratio (OR): 1.616, 95% confidence interval (CI): 1.055–1.901, p < 0.001], multivessel disease (OR: 1.913, 95% CI: 1.545–2.091, p < 0.001), and SYNTAX score > 22 (OR: 1.817, 95% CI: 1.438–2.253, p < 0.001). Table 3 shows the independent predictors of stenotic CAD, multivessel disease and SYNTAX score > 22 in multivariate analysis.

Discussion

The main finding of the present article was that the SCORE may be useful to predict patients with more severe CAD and patients at relatively high risk for future cardiovascular events, even in the absence of high risk features according to SCORE system.

Table 1. Clinical, laboratory, and angiographic characteristics of patients according to Systematic Coronary Risk Evaluation (SCORE)

	SCORE < 1% (n = 171)	SCORE ≥ 1% and < 5% (n=281)	p
Age (years)	44.5 ± 2.39	52.5 ± 5.51	< 0.001
Gender			
Male n (%) Female n (%)	33 (19.3%) 138 (80.7%)	191 (68%) 90 (32%)	< 0.001
Smoking n (%)	32 (18.7%)	108 (38.4%)	< 0.001
LVEF (%)	62.2 ± 3.76	61.9 ± 3.78	0.375
SBP [mm Hg]	143.5 ± 9.07	149 ± 12.5	< 0.001
DBP [mm Hg]	84.5 ± 7.86	89.6 ± 6.93	< 0.001
WBC count [× $10^3/\mu L$]	7.55 ± 1.39	7.62 ± 1.34	0.867
Platelet count [×$10^3/\mu L$]	248 ± 58.7	258 ± 62.9	0.109
Hemoglobin [g/dL]	12.1 ± 1.52	13.4 ± 1.94	< 0.001
Creatinine [mg/dL]	0.8 ± 0.14	0.8 ± 0.15	0.122
AST [U/L]	21.9 ± 8.61	22.6 ± 8.29	0.741
Total cholesterol [mg/dL]	183 ± 35.8	211 ± 38.4	< 0.001
LDL-cholesterol [mg/dL]	93.6 ± 21	118 ± 34.2	< 0.001
HDL-cholesterol [mg/dL]	45.2 ± 6.89	38.6 ± 8	< 0.001
Stenotic CAD	60 (35.1%)	159 (56.6%)	< 0.001
Multivessel disease	16 (9.4%)	74(26.3%)	< 0.001
SYNTAX score	5.18 ± 7.07	13.5 ± 9.32	< 0.001

LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; DBP — diastolic blood pressure; WBC — white blood cell; AST — aspartate aminotransferase; LDL — low-density lipoprotein; HDL — high-density lipoprotein; CAD — coronary artery disease

Table 2. Patients' characteristics according to SYNTAX score

	SYNTAX score ≤ 22 (n = 155)	SYNTAX score > 22 (n = 64)	p
Age [y]	51.4 ± 6.33	53.9 ± 5.08	0.005
Gender			
Male n (%) Female n (%)	76 [49%] 79 [51%]	50 (78.1%) 14 (21.9%)	< 0.001
SCORE (%)	1.75 ± 1.38	3.48 ± 1.26	< 0.001
Smoking n (%)	60 (38.7%)	24 (37.5%)	0.867
LVEF (%)	62.6 ± 4.04	61.8 ± 2.04	0.325
SBP [mm Hg]	151 ± 9.84	158 ± 10.04	< 0.001
DBP [mm Hg]	91.9 ± 5.75	97 ± 5.47	< 0.001
WBC count [× $10^3/\mu L$]	8.09 ± 1.50	7.92 ± 1.02	0.127
AST [U/L]	19.3 ± 9.06	21.5 ± 5.8	0.078
Platelet count [× $10^3/\mu L$]	235 ± 46.4	284 ± 84.8	< 0.001
Hemoglobin [g/dL]	12.8 ± 1.82	14.4 ± 1.42	< 0.001
Creatinine [mg/dL]	0.8 ± 0.13	0.8 ± 0.14	0.181
Total cholesterol [mg/dL]	212 ± 35.2	226 ± 49.2	0.019
LDL-cholesterol [mg/dL]	117 ± 26.9	134 ± 48.4	< 0.001
HDL-cholesterol [mg/dL]	38.8 ± 7.12	33 ± 6.22	< 0.001

SCORE — Systematic Coronary Risk Evaluation; LVEF — left ventricular ejection fraction; SBP — systolic blood pressure; DBP — diastolic blood pressure; WBC — white blood cell; AST — aspartate aminotransferase; LDL — low-density lipoprotein; HDL — high-density lipoprotein

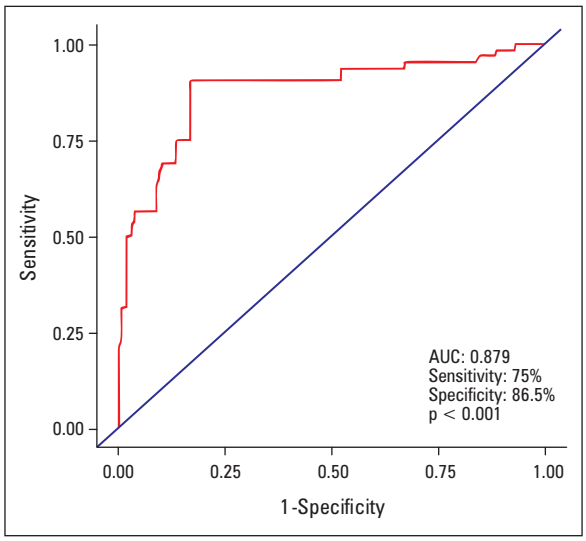

Figure 1. Receiver operating characteristic (ROC) curve analysis of Systematic Coronary Risk Evaluation (SCORE) to predict SYNTAX score > 22

Therefore, the results of our study may be helpful for further risk stratification of hypertensive patients, in particular, for patients without high risk features and with suspected CAD. To our knowledge, this is the first study to report an independent relationship between SCORE and CAD severity in hypertensive patients with low and moderate risk based on SCORE system.

There is a consistent link between increased blood pressure and coronary atherosclerosis, and hypertension is the most important modifiable risk factor for development and progression of CAD, from endothelial dysfunction to symptomatic obstructive CAD [10, 11]. Atherosclerosis is the leading cause of morbidity and mortality in hypertensive patients; however, the hypertension related coronary atherosclerosis generally requires a silent long process, and once CAD is emerged, it affects prognosis independently [4, 12]. Hereby, early and accurate risk stratification remains the cornerstone of the implementation of preventive treatments in hypertensive subjects.

SCORE system is a useful tool in clinical practice considering multiple traditional cardiovascular risk factors, and is essential in the risk stratification of hypertensive patients [4, 6]. Nevertheless, the SCORE system mainly estimates only 10-year risk of a first fatal atherosclerotic cardiovascular event, and its predictive value regarding non-fatal events is not well described. However, due to the nature of the SCORE system consisting five important risk factors for CAD, it is reasonable to consider that it may be associated with various cardiovascular end points, and may be more helpful than expected in clinical practice.

Since the combination of the traditional cardiovascular risk factors predicts atherosclerosis more accurately, risk scores play an essential role in the estimation of total cardiovascular risk and subsequent implementation of preventive managements [13]. Cardiovascular risk scores including SCORE system have been shown to be associated with CAD severity in small studies conducted in unselected patients underwent coronary angiography, mainly due to high risk features [14–16]. However, no study investigated the association of SCORE system with CAD severity in isolated hypertensive patients with low and moderate risk. We determined a significant positive correlation between SCORE and CAD severity, and also found that hypertensive patients at moderate risk had significantly more severe CAD compared to those at low risk according to SCORE

Table 3. Multivariate logistic regression analysis for independent predictors of stenotic coronary artery disease (CAD), multivessel disease and SYNTAX score > 22

Variable	OR	95% CI	p
Stenotic CAD			
SCORE	1.616	1.055–1.901	< 0.001
LDL-cholesterol	1.162	1.034–1.290	< 0.001
DBP	1.068	1.040–1.130	< 0.001
Multivessel disease			
SCORE	1.913	1.545–2.091	< 0.001
LDL-cholesterol	1.171	1.098–1.570	< 0.001
SYNTAX score > 22			
SCORE	1.817	1.438–2.253	< 0.001
LDL-cholesterol	1.079	1.037–1.492	< 0.001

CAD — coronary artery disease; SCORE — Systematic Coronary Risk Evaluation; LDL — low-density lipoprotein; DBP — diastolic blood pressure; OR — odds ratio; CI — confidence interval

system. Hereby, our results point out the importance of further risk assessment of hypertensive patients, even if they are considered as low or, in particular, moderate risk according to SCORE system.

The main clinical importance of risk assessment by SCORE is its essential role in the providing successful prevention of future events [4, 6]. Primary prevention methods including drug treatment reduce major cardiovascular events in patients at high risk or very high risk according to SCORE (SCORE ≥ 5%) [6, 17]. Hence, these patients generally receive optimal preventive treatments without need for further risk assessment. However, preventive treatment with drugs are not generally recommended for patients at low to moderate risk (SCORE < 5%), and these patients are usually offered lifestyle advice to maintain their low to moderate risk status [6]. On the other hand, the findings of the present article suggest that a selected subgroup of hypertensive patients at moderate risk according to SCORE system may be considered as patients at relatively high risk and may provide more benefit from preventive treatments. Consequently, widening the preventive methods for hypertensive patients with suspected CAD and at moderate risk according to SCORE system may be useful for an optimal primary prevention. Nevertheless, there is lack of data regarding the clinical benefit of preventive treatments in moderate risk hypertensive patients, and future studies investigating this topic are necessary. In this sense, the key point of the present study is that SCORE may be useful for further risk stratification in hypertensive patients even in the absence of high risk features.

The present study has some limitations. First, the study included a selected patient population between the age 40 and 65. Therefore, it is difficult to generalize our findings to hypertensive patients that are out of this age range. However, the SCORE system is validated for hypertensive subjects between the age 40 and 65, and this age range includes the vast majority of patients that will benefit from the preventive treatments. Second, although we excluded the patients with asymptomatic hypertension-mediated organ damage, there may be still some other clinical factors that increase the patients' risk independently.

Conclusions

The SCORE system may be useful in further risk stratification of hypertensive patients who have moderate risk features and are suspected of CAD. Our study suggests that SCORE has an independent relationship and positive correlation with SYNTAX score, in particular in patients at moderate risk, which may affect the prognosis independently. Therefore, SCORE may be useful in the discrimination of hypertensive patients at relatively high risk even if they are assigned as moderate risk according to SCORE system. Further risk assessment in this selected subgroup of hypertensive patients with suspected CAD may lead a more adequate preventive program and treatment.

Conflict of interest

Nothing to declare — we have no commercial, financial, and other relationships in any way related to the subject of this article that might create any potential conflict of interest.

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Objective measurement of physical activity in a random sample of Saint-Petersburg inhabitants

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Abstract

Background: World Health Organization (WHO) experts listed physical inactivity in leading risk factors for global mortality. Current research shows that only objective measurement of physical activity may provide accurate information on this parameter. The aim of our study was to assess the 7-day physical activity monitoring using triaxial accelerometers in a random sample of Saint-Petersburg inhabitants.

Material and methods: As a part of all-Russian epidemiology survey ESSE-RF there was involved random sampling of 1600 Saint-Petersburg inhabitants (25–65 years) stratified by age and sex. After that a random sub-population of 100 subjects was selected. All subjects filled in questionnaire regarding physical activity, occupation, education and nutrition. Anthropometry (weight, height with body-mass index calculation, waist circumference) was performed. Actigraph GT3X+ (Actigraph LLC, USA) accelerometer and physical activity diary were used in order to evaluate physical activity monitoring for 7 days. Adequate levels of physical activity (PA) were defined as more than 10 000 steps/day and at least 150 minutes/week of moderate and vigorous physical activity (MVPA) in bouts of 10 minutes or more.

Results: 1/2 of subjects were physically active according to steps, and 1/3 according to MVPA time criteria. No gender, occupation or body composition differences were revealed in physically active and inactive subjects. Almost 50% of physically active subjects had balanced workweek-weekend PA profile, and the same criterion is true only for 13% of subjects in inactive group. In both groups the same peaks of MVPA were revealed — at 8.00–9.00 and 18.00–19.00, which are typical transportation time, but in active group these peaks were significantly higher. According to PA diaries, in most of cases physical inactivity was related to the usage of private or public transport.

Conclusion: Triaxial PA-monitoring shows, that 40–60% of subjects were physically inactive, and 150-min MVPA goal can easily be achieved by only increasing walking time during transportation peaks. The physical inactivity was not determined by the type of occupation, sex or age, instead it was mainly influenced by the usage of cars in the morning and evening transportation time, rather than walking.

Key words: physical activity level; hypodynamia; triaxial accelerometer; objective measurement

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Introduction

Level of physical inactivity is rising in many countries with possible major implications for the general health of people and for the prevalence of noncommunicable diseases (NCD) such as cardiovascular diseases, diabetes, cancer and related risk factors (elevated blood pressure, impaired glucose metabolism, overweight). World Health Organization (WHO) experts identified physical inactivity as the fourth leading risk factor for global mortality [1]. Physical inactivity is estimated to be the principal cause for approximately 21–25% of breast and colon cancer burden, 27% of diabetes and approximately 30% of ischemic heart disease burden [1]. According to literature review [2–4], there is a dose-response relation between intensity, frequency, duration and volume of physical activity (PA) and NCD risk. World Health Organization recommendations indicate that 150 minutes per week of moderate- to vigorous-intensity physical activity (MVPA), accumulated in short multiple bouts of at least 10 minutes, or one long bout may lead to NCD reduction. Recent studies showed, that use of accelerometers may provide accurate information on not only PA related energy expenditure and PA intensity, but also may objectively calculate consecutive minutes in MVPA during leisure time activity, which is almost impossible with PA self-reports.

Although some studies including objective PA-measurement were performed in Russia, most of them used pedometers and none of them used triaxial accelerometers in a random population-based sample. It was shown that waist-mounted, uniaxial accelerometer, with cut points based on walking, misses some physical activity and triaxial devices tend to have higher correlations with energy expenditure [5].

The aim of our study was to assess a 7-day physical activity monitoring using triaxial accelerometers in a random sample of Saint-Petersburg inhabitants.

Material and methods

As a part of the nationwide Russian epidemiologic survey ESSE-RF a random sampling of 1600 Saint-Petersburg inhabitants (25–65 years) stratified by age and sex was involved. A random sub-population of 100 subjects was subtracted from the initial sample, according to the age and sex distribution. On the day of recruitment, participants underwent anthropometric, behavioral and biochemical assessments, including fasting lipids and glucose levels (ARCHITECT (USA), Abbott). Socio-economic (including education and occupation), behavioral attributes as well as information on medical conditions and therapy were assessed using questionnaires administered by trained interviewers who utilized standard protocols (which were described before [6]). The trained personnel conducted height, weight, waist circumference and resting blood pressure measurements according to standard protocols.

For the physical activity monitoring all subjects were asked to wear an Actigraph GT3X+ (Actigraph LLC, USA) accelerometer for 7 days over the right hip on an elastic belt while they were awake and on the right wrist during sleep time. Participants were also asked to fill in a 7–days diary regarding their physical activity during time of investigation. Data were recorded with 100 Hz on three axes and then aggregated to 10-second epochs. Accelerometer data were obtained from 100 individuals. A valid measurement was defined as having at least 5 days with a minimum of 10 hours monitor wear. Wear time was determined by subtracting non-wear time from 24 hours. Non-wear was defined as zero activity intensity counts for 1 minute, or 0–99 counts for maximum 2 minutes. The amount of physical activity measured by accelerometer was presented according to number of steps and by the time spent in moderate and vigorous physical activity. Time spent in physical activity of moderate or vigorous intensity, separately or combined, was based on application of count thresholds corresponding to moderate- or vigorous-intensity activity. Intensity-threshold criteria were 1952–5724 counts for moderate intensity (equivalent to 3 METs) and 5725–9498 counts for vigorous intensity (6 METs). Time spent in activity of a defined intensity (moderate, vigorous, or moderate and vigorous combined) was determined by summing up minutes of a day where the count met the criterion for the respective intensity. Moderate to vigorous physical activity (MVPA) duration data was also presented in sustained bouts, in accordance with physical activity recommendations, where 10-min MVPA bouts were defined as 10 or more consecutive minutes above the relevant threshold. Mean daily time in bouts was calculated across all valid days.

Adequate levels of physical activity were defined in 3 ways — according to number of steps — more then 10 000 steps/day; according to time, spent in moderate and vigorous physical activity — more than 300 minutes/week; according to time of moderate and vigorous physical activity in bouts of 10-minutes or more — at least 150 minutes/week [7].

Physical activity was defined as balanced when participants spent 20–35% of their MVPA time in 10-min bouts on weekend (Saturday and Sunday);

less than 20% of MVPA on the weekend was defined as main physical activity during workweek (from Monday to Friday), and more than 35% of MVPA on the weekend as main physical activity on weekend.

The definition of occupational categories was performed, according to the data from the questionnaire. Subjects with intellectual type of occupation were defined as "intellectual group", manual workers were defined as "manual group", and other subjects (including retired participants) were defined as "average group".

Statistical analysis was performed by statistical package SSPS Statistics 20 (IBM, USA). The sex-specific characteristics of the sample were obtained by simple tabulations and descriptive statistics. Differences for continuous variables among the subgroups were assessed by one-way ANOVA. Multiple pairwise comparisons were made with a post hoc Scheffe test; the significance level of the p-value was reduced to 0.005.

Results

After random selection of 100 subjects in accordance with the age-sex distribution of the initial sample, accelerometer measurements were performed. Because of too long non-wear period 7 subjects were excluded. The final sample included 39 males and 54 females. The percentage of physically active subjects were determined in accordance with the 3 criteria mentioned above, in males and females, in 4 age groups (25–34 y.o., 35–44 y.o., 45–54 y.o. and ≥ 55 y.o.) and among obese (BMI ≥ 30 kg/m^2) and non-obese (BMI < 30 kg/m^2) subjects — results are presented in Table 1.

Mean number of steps/week and average time in 10-minute MVPA bouts/week were calculated among physically active and inactive subjects (according to steps/day criteria and time in 10-min MVPA bouts criteria) and in subjects of different occupational categories. Surprisingly, no significant differences in number of steps or MVPA time were found across the occupational categories – results are shown in Table 2.

The seven-day wear time protocol provided the possibility to discriminate workweek and weekend days. In Figure 1, it can clearly be seen that physically active subjects (according to 10-min bouts criteria) are more active during the whole week (35–53 minutes of MVPA/day, including the weekend). The non-active group accumulated about 8–12 MVPA minutes/day, and they are even less active on weekends.

Comparing time in 10-min bouts of MVPA on workweek and weekend for every participant, physically active subjects (Fig. 2) have more balanced PA

Table 1. Proportions of physically active subjects according to different optimal physical activity (PA) criteria depending on age, gender and anthropometric features

	N of subjects	> 10 000 steps/day	> 300 min/week in MVPA	> 150 min/week in 10-min bouts of MVPA
All	93	57%	70%	37%
Age				
25–34 y.o.	21	52%	70%	41%
35–44 y.o.	17	46%	69%	61%
45–54 y.o.	26	40%	64%	32%
≥ 55 y.o.	29	35%	82%	32%
p between age groups		0.53	0.51	0.61
Sex				
Males	39	48%	63%	39%
Females	54	38%	78%	38%
p males *vs.* females		0.24	0.28	0.54
BMI				
< 30 kg/m^2	57	44%	69%	38%
≥ 30 kg/m^2	36	36%	76%	36%
p obese *vs.* non-obese		0.33	0.38	0.53

MVPA — moderate- to vigorous-intensity physical activity; BMI — body mass index

Table 2. Number of steps and time in 10-min bouts of moderate- to vigorous-intensity physical activity (MVPA) during 1 week in subjects with different physical activity (PA) status and occupation

	Steps count	SE	Time 10 min bouts	SE
< 10 000 steps/day (n = 28)	51027.46	2422.54	92.26	10.32
≥ 10 000 steps/day (n = 65)	95215.21	5012.62	230.14	22.87
p	**< 0.001**		< 0.001	
< 150 min in 10min bouts (n = 40)	54321.43	2625.55	65.74	5.96
≥ 150 min in 10min bouts (n = 53)	94108.03	5850.78	285.19	14.44
p	**< 0.001**		< 0.001	
Intellectual group (n = 29)	78503.58	9829.99	176.09	31.07
Manual group (n = 33)	78204.43	6034.73	152.71	36.24
Average group (n = 31)	64170.78	4789.04	140.78	19.60
p	**0.72**		0.43	

SE — standard error

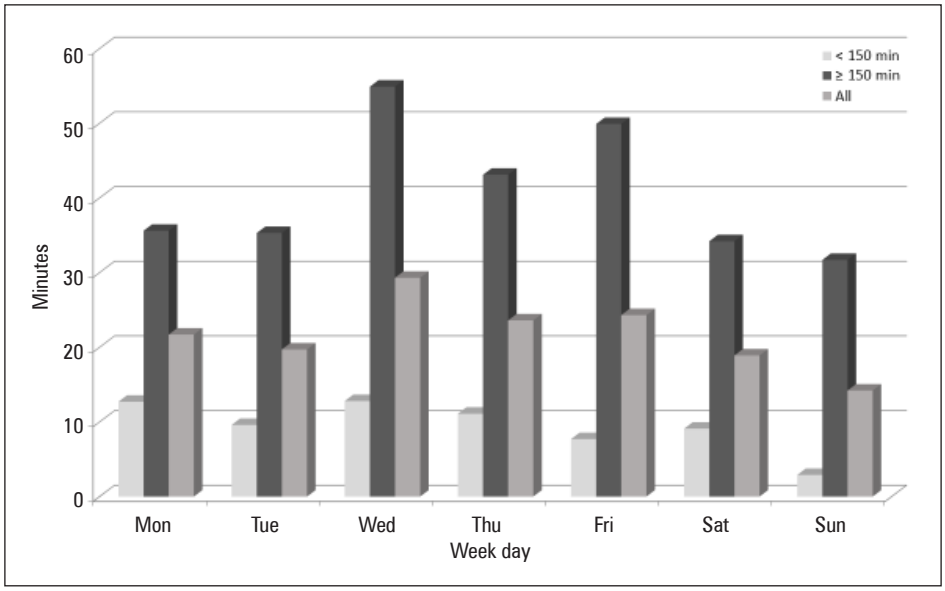

Figure 1. Seven-day pattern of time in 10-min bouts of moderate- to vigorous-intensity physical activity (MVPA) in subjects with different physical activity (PA) status

profile during whole week, i.e. 42% of them have same levels of physical activity on workweek and weekends, 42% are more active during workweek and 16% — on weekend.

Only 13% of inactive participants have balanced MVPA bouts during the week, 70% of them are mainly active during workweek and 17% — on weekend (Fig 3).

Describing a typical day of physically active and physically inactive subjects (according to 10-min MVPA bouts criteria) in both groups we can see the same peaks of MVPA at 8.00–9.00 and 18.00–19.00 time, which are the periods of typical home-to-work and work-to-home transportation. Some optimal PA subjects have MVPA episodes during work time (at 12.00–13.00 and at 15.00) independently of type of occupation, but from Figure 4 it can clearly be seen, that subjects who are physically active are more active on their transportation time and during whole work time.

Discussion

This study provides first Russian results of 7-day objective measurement of physical activity duration and intensity using triaxial accelerometers. According to all three criteria of optimal PA level, no signifi-

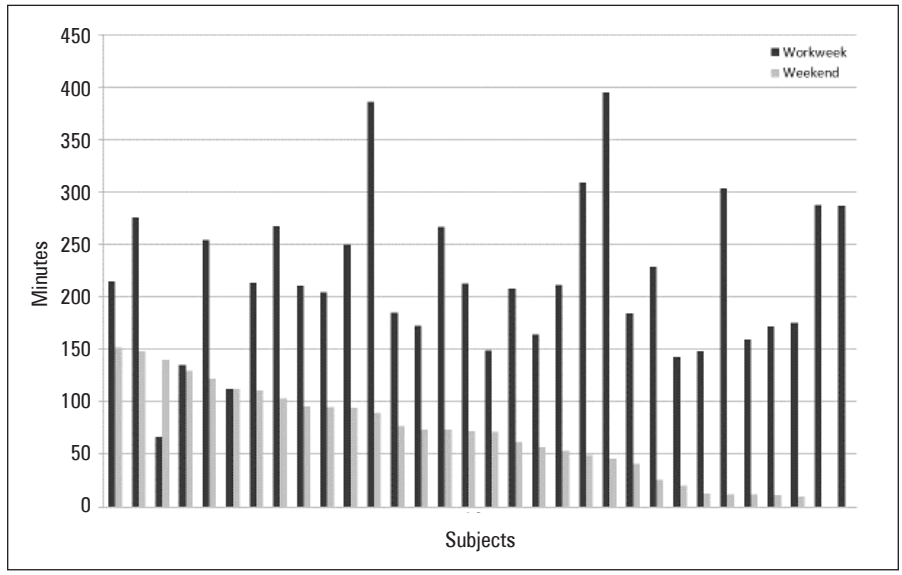

Figure 2. Comparison of time in 10-min moderate- to vigorous-intensity physical activity (MVPA) bouts on workweek and weekend in subjects with adequate level of physical activity (PA)

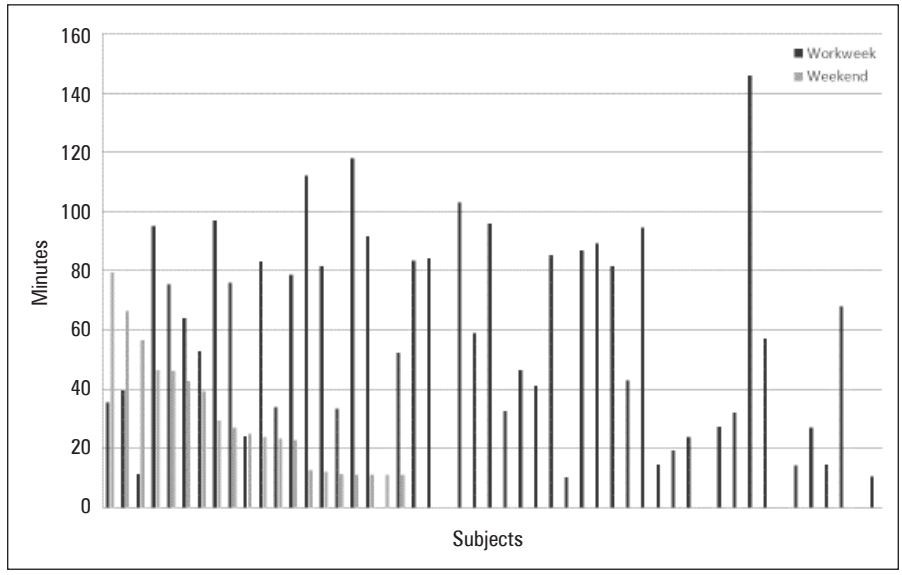

Figure 3. Comparison of time (minutes) in 10-min moderate- to vigorous-intensity physical activity (MVPA) bouts on workweek and weekend in subjects with non-optimal level of physical activity (PA)

cant differences were found between four age groups, males and females or obese and non-obese subjects. Occupation also showed no influence on the physical activity status. Main MVPA-providing period was morning and evening transportation time, and physical inactive behavior may be associated with an increased use of private or public cars on 15-min walking distances.

Since the mid-1980s, there has been a steady increase in data concerning association of physical activity levels with risk of non-communicable diseases, such as type 2 diabetes, obesity, and cardiovascular disease [8]. Previous publications have shown that self-reported physical activity time and intensity may be completely inaccurate [9]. Nowadays, it is clear that movement sensors, such as pedometers and accelerometers, may overcome most of the problems related to self-report [10]. While pedometers are specifically designed to measure features of walking behaviors such as total steps taken per day [11], accelerometer-based physical activity monitors allow researchers to track frequency, in-

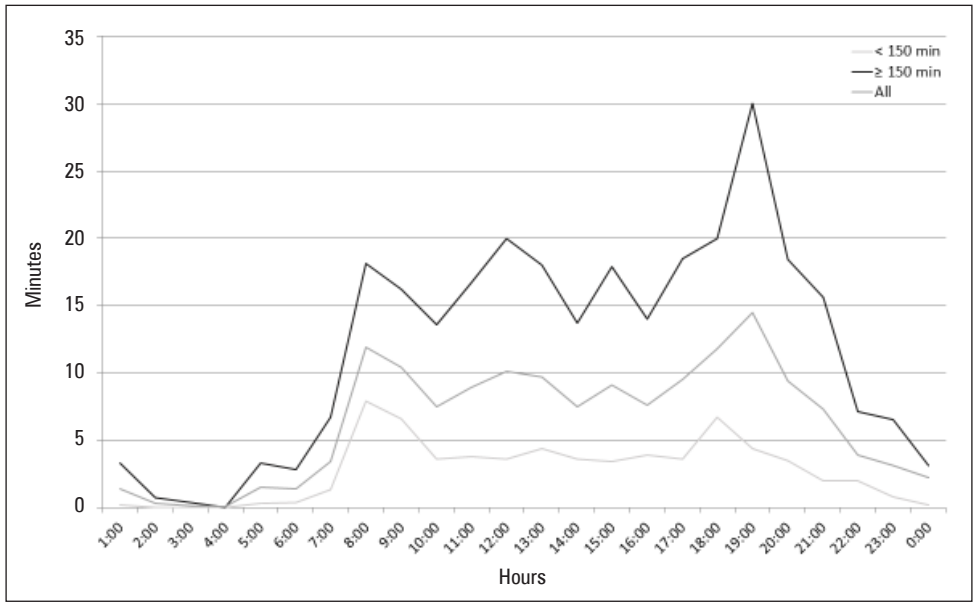

Figure 4. Physical activity (PA) (in minutes) of moderate- to vigorous-intensity physical activity (MVPA) during average 24-hour period in subjects with different PA levels

tensity, and duration of activity [12]. Prior to the development of triaxial accelerometers, uniaxial accelerometers were used to measure accelerations that occurred within the vertical plane [13]. Triaxial accelerometers capture movement in all 3 orthogonal planes. As a result, these devices provide the opportunity to capture many more activities than uniaxial accelerometers; thus, in comparison with uniaxial instruments, the output from triaxial devices tends to have higher correlations with energy expenditure [14]. Therefore, using of triaxial accelerometers may help to avoid bias of self-reported physical activity measurement, give new information on correlations between physical activity level and risk factors for non-communicable diseases and help to update modern PA recommendations.

According to WHO recommendations, NCD-risk reductions routinely occur at levels of at least 150 minutes of moderate-intensity activity per week, achieved through accumulation of bouts of 10 or more consecutive minutes [15]. But it is important to recognize that the current recommendations [8, 15] are based on epidemiological data concerning association between self-reported physical activity and health outcomes [4, 8, 15]. Because of low consistency of self-reported and objectively measured physical activity levels in big studies, like NHANES in USA [16], the need to change PA recommendations was discussed. According to PA diary and actigraphy with triaxial accelerometers, performed in our study, it can clearly be seen, that main physical activity is performed with walking, as in other studies [16]. Analyzing 10-min MVPA bouts during whole week, it was shown, that the majority of subjects with optimal (> 150 min of MVPA/week) level of PA have a balanced workweek-weekend profile, so this participants are active every day independently of sex, BMI or occupation. On the other hand, inactive subjects have lower levels of MVPA during workweek and even less activity on weekend. According to PA diary, filled in during PA monitoring by every participant, it may be explained mainly with use of personal or public cars for transportation and lack of compensating self-trainings on weekends. Physical activity profile during an average day is similar in both active and non-active subjects — there are two main PA peaks in morning and evening time, describing episodes of home-to-work transportation. In the physically active group, average time in MVPA on these peaks is 15 minutes in the morning and 20–30 minutes in the evening — walking time from place of work to metro or other destination point, according to PA diaries. There are the same peaks in non-active group, but much lower — about 7 minutes, mainly caused by using cars on most days, according to PA diary.

The results of triaxial PA-monitoring in the random sample of Saint-Petersburg inhabitants demonstrate, that 150-min MVPA goal can easily be achieved by increasing walking time in two natural home-to-work and work-to-home transportation peaks on workweek and some additional exercises on weekend. According to PA-monitoring and diary information, main reason for lack of physical activ-

ity cannot be found in the type of occupation, sex or age, but in the use of cars in morning and evening transportation time, instead of walking.

Competing interests

No potentially competing interests are declared.

Financial disclosure

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Ethics statement

The study has been approved by the Ethics Committee of Almazov National Medical Research Centre, Saint Petersburg, Russia. Written informed consent was provided by all patients. All medical data used in this study have been anonymized.

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