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PREVALENCE OF DIABETIC NEPHROPATHY

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Key words: diabetic nephropathy, outcome, risk factors

SUMMARY

In this review, we try to highlight the prevalence of diabetic nephropathy which is not uncommon complication of diabetes all over the world. We aimed to give short hints on stages of diabetic nephropathy, the possible identified risk factors for kidney disease in diabetes (both type 1 and type 2) and its progression. We have reviewed around 70 papers concerning the issue of diabetic nephropathy and the possible risk factors for progression and potential regression in both type 1 and 2 diabetes mellitus. Moreover, we added a few paragraphs about diabetic nephropathy in different countries of the world and in geriatric population.

INTRODUCTION

Diabetic nephropathy is a serious complication that occurs in 20% to 40% of all diabetics. In the Western world, diabetic nephropathy is the primary single cause of end-stage kidney disease (ESKD) (1). Both type 1 and type 2 diabetes mellitus (DM) can lead to nephropathy, but in type 2 DM, a smaller proportion of patients progress to ESKD. Because of the higher prevalence of type 2 DM, these patients represent more than half of diabetics on dialysis (2). The incidence of diabetic nephropathy as a cause of ESKD is increasing each year (1). For clinical care and epidemiological studies, diabetic kidney disease (DKD) is defined by elevated urine albumin excretion or reduced glomerular filtration rate (GFR), or both (3).

The prevalence of diabetes around the world has reached epidemic proportions. While diabetes is already estimated to affect more than 8% of the global population (nearly more than 350 million people), it is predictable to grow to over 550 million people by the year 2035 (4). It has been estimated that more than 40% of people with diabetes will develop chronic kidney disease (5) including a significant number of
those who will develop ESKD requiring renal replacement therapies (dialysis and/or transplantation).

Diabetic nephropathy is uncommon if diabetes is of less than 10-year duration. The peak incidence rates of 3% per year are on average seen 10 to 20 years after diabetes onset, after which the rate of nephropathy tapers off. It is worth saying that a diabetic patient free from clinical signs of nephropathy for 20 to 25 years has only 1% yearly chance of developing such a complication (6). There is marked racial/ethnic and international discrepancy in the epidemiology of diabetic nephropathy (7, 8). Native Americans, Hispanics (especially Mexican Americans) and African Americans have a much higher risk of developing ESKD than non-Hispanic whites with type 2 diabetes (7). Based on 2002 United States (US) data, diabetes is the cause of renal disease in 44% to 45% of incident ESKD cases, making the US rate one of the highest worldwide (8). Internationally, there is considerable variability among countries, with percentages ranging from 9% in Russia to 49% in Malaysia. This discrepancy could be explained by differences in economic viability and governmental infrastructures (9).

STAGES OF DIABETIC NEPHROPATHY

Diabetic nephropathy is a chronic complication of both type 1 DM (beta cell damage, absolute lack of insulin) and type 2 DM (insulin resistance and/or decreased insulin secretion) (10). There are five stages in the development of diabetic nephropathy: stage I, glomerular filtration rate (GFR) is either normal or increased; it lasts for around five years from the onset of DM. The size of the kidneys is increased by nearly 20% and renal plasma flow is increased by 10%-15%, but without albuminuria or hypertension; stage II starts more or less two years after the onset of the disease with thickening of basement membrane and mesangial proliferation with normalization of GFR but without clinical signs of the disease. Many patients remain in this stage until the end of their life; stage III represents the first clinically detectable sign of glomerular damage and microalbuminuria (albumin 30-300 mg/day). It usually occurs five to ten years after the onset of the disease with or without hypertension. Approximately 40% of patients reach this stage; stage IV is the stage of chronic kidney disease (CKD) with irreversible proteinuria (>300 mg/day), decreased GFR below 60 mL/min/1.73 m², and sustained hypertension; and stage V is defined when ESKD with GFR <15 mL/min/1.73 m² is detected. Nearly 50% of patients require kidney replacement therapy (peritoneal dialysis, hemodialysis or kidney transplantation) (11). In the early stages of diabetic nephropathy, nephromegaly and changed doppler indicators may be the early morphological signs of renal damage, however, proteinuria and GFR are the best indicators of the damage degree (12).

The predictive value of microalbuminuria for the development of kidney damage in patients with type 1 or type 2 DM was confirmed in the early 1980’s (13). Approximately 20%-30% of the patients develop microalbuminuria after 15 years of disease duration and less than half develop real nephropathy (14). The European Diabetes (EURODIAB) Prospective Complications Study Group (15) and 18-year Danish study (16) report overall occurrence of microalbuminuria in patients with type 1 and type 2 DM as 12.6% (after 7.3 years) and 33%, respectively. According to the United Kingdom Prospective Diabetes Study (UKPDS), the annual incidence of microalbuminuria in patients with type 1 and type 2 DM as 12.6% (after 7.3 years) and 33%, respectively. According to the United Kingdom Prospective Diabetes Study (UKPDS), the annual incidence of microalbuminuria in patients with type 2 DM in Great Britain is 2% and the prevalence is 25% ten years after the diagnosis (8). Proteinuria develops more frequently in patients with type 1 diabetes (15%-40%), usually after 15-20 years of DM duration (17), but in patients with type 2 DM, the prevalence varies between 5% and 20% (4).

RISK FACTORS FOR KIDNEY DISEASE IN TYPE 1 DIABETES

Hyperglycemia is a well known risk factor for DKD and it has been recognized that intensive glucose control reduces the risk of DKD (4). Specifically, during the Diabetes Control and Complications Study (DCCT), near normalization of blood sugar decreased the risks of incident microalbuminuria and
Macroalbuminuria by 39% (95% CI 21%-52%) and 54% (95% CI 29%-74%), respectively, compared with conventional therapy. Even with long-term follow up in the observational Epidemiology of Diabetes Interventions and Complications (EDIC) study, participants previously assigned to DCCT intensive therapy continued to experience lower rates of incident microalbuminuria and macroalbuminuria with risk reductions of 45% (95% CI 26%-59%) and 61% (95% CI 41%-74%), respectively (18). Beneficial effects of intensive therapy on the worsening of GFR have become evident during long-term combined DCCT/EDIC follow up, with risk reduction of 50% (95% CI 18%-69%). Other risk factors for DKD in diabetics include male sex, obesity, hypertension, inflammation, insulin resistance, vitamin D deficiency, and dyslipidemia (4, 8, 19). Moreover, a hereditary component in DKD has long been recognized as some genetic loci and polymorphisms in specific genes have been associated with DKD.

**DIABETIC KIDNEY DISEASE IN TYPE 1 DIABETES**

During the last century, landmark studies of type 1 DM considered the natural history of DKD as progressive increase of urine albumin excretion, followed by GFR loss and development of ESKD. Microalbuminuria was defined as albumin excretion rate (AER) 30 to 299 mg/24 h (‘incipient nephropathy’) progressing steadily to macroalbuminuria with AER ≥300 mg/24 h (‘diabetic nephropathy’). Microalbuminuric patients commonly noted to have higher GFR ‘hyperfiltration’, while macroalbuminuric patients showed rapid GFR loss leading steadily to ESKD. Frequent exceptions were observed. Specifically, albuminuria was observed to revert, while GFR loss was observed without albuminuria and was not always progressive. Therefore, albuminuria and impaired GFR are not necessary complementary, overlapping manifestations of DKD (4).

**INCIDENCE OF KIDNEY DISEASE IN TYPE 1 DIABETES**

Nearly half (or slightly less) of patients with type 1 DM develop DKD during their lifetime. Albuminuria and reduced GFR (<60 mL/min/1.73m²) are rare during the first decade of type 1 DM diagnosis (4). In more recent studies, the lifetime cumulative incidence of macroalbuminuria has been described as 15%-25%, and the cumulative incidence of microalbuminuria has been reported as 25%-40% (19). In early studies, up to 35% of participants developed ESKD. In Finland and in the Pittsburgh Epidemiology of Diabetes Cohort (Pittsburgh, PA, USA), the long-term cumulative incidence of ESKD dropped to less than 10%, although the rate of ESKD remained higher in the Joslin type 1 diabetes cohort (Boston, MA, USA) (20).

**PROGRESSION OF KIDNEY DISEASE IN TYPE 1 DIABETES**

The progression of DKD in type 1 DM is unpredictable. In the Joslin type 1 diabetes cohort, 29% of participants with microalbuminuria showed reduced GFR within 12-year average follow up. The EURODIAB type 1 diabetes study has reported that 14% of microalbuminuric patients progressed to macroalbuminuria over 7.3-year average follow-up. Steno type 1 diabetes cohort showed that 34% of participants with microalbuminuria went on to develop macroalbuminuria over 7.5-year average follow up (19). In the DCCT/EDIC cohort, the 10-year cumulative incidence of macroalbuminuria was 28% in the participants who had incident microalbuminuria (20).

In the DCCT/EDIC cohort, patients with macroalbuminuria lost GFR at a mean rate of 5.7% per year, and the 10-year cumulative incidence of impaired GFR was 32%, while in patients with microalbuminuria, the mean rate of estimated GFR loss was 1.2% per year, and the 10-year cumulative incidence of reduced GFR was 15%. Interestingly, in the Joslin type 1 diabetes cohort, the “early renal function decline” occurred in 31% of participants with microalbuminuria and occasionally also in participants...
with persistent normoalbuminuria (AER <30 mg/24 h). Such findings suggest that albuminuria and GFR loss are linked but are not necessarily reflective of a single, homogeneous underlying disease process (8).

REGRESSION OF KIDNEY DISEASE IN TYPE 1 DIABETES

Microalbuminuria commonly regresses to normoalbuminuria as reported in the Joslin type 1 diabetes cohort. The authors showed that 58% of patients with persistent microalbuminuria regressed to persistent normoalbuminuria over the next 6 years, frequently without inhibitors of the renin-angiotensin-aldosterone system (RAAS) (19). Similar results were observed in the DCCT/EDIC (8, 19). Therefore, better control of diabetes, hypertension and lipids was associated with a greater likelihood of microalbuminuria regression. Of the DCCT/EDIC participants who developed macroalbuminuria, 52% regressed to sustained microalbuminuria or normoalbuminuria within 10 years, but many were managed with RAAS inhibitors (21). Moreover, regression of macroalbuminuria was associated with an 89% lower risk of progressing to reduced GFR. In the same direction, longitudinal studies of pancreas transplantation demonstrate that the pathological lesions of diabetic glomerulopathy can regress with euglycemia (22).

KIDNEY DISEASE IN TYPE 2 DIABETES

The incidence of DKD and the rates of DKD progression are less clear in type 2 DM compared with type 1 DM, mainly due to the highly variable age at onset, complexity of defining the exact time of diabetes onset, and the relative scarcity of long-term type 2 diabetes cohorts. Therefore, two of the best characterized type 2 DM cohorts are the United Kingdom Prospective Diabetes Study (UKPDS) and the Pima Indian population. The UKPDS enrolled more than 5000 participants with new-onset type 2 DM and after a median 15-year follow up, they found that microalbuminuria (defined as persistent urine albumin concentration ≥50 mg/L) occurred in 38% and reduced GFR (defined as persistent estimated creatinine clearance ≤60 mL/min/1.73m²) in 29% of participants (23). Among Pima Indians, for whom the onset and duration of diabetes are more precisely determined due to systematic diabetes screening, the cumulative incidence of heavy proteinuria (≥1 gram per gram creatinine) was 50% at 20-year duration, prior to widespread use of RAAS inhibitors. The high rate of proteinuria in the Pima population remained stable over time, although the incidence of ESKD had declined (24).

In most type 2 diabetics, the prevalence of DKD at any time point is approximately 30%-50%. Among the US adults with diabetes (>90% type 2), the overall prevalence of DKD was approximately 35%, ranging from nearly 25% in patients younger than 65 to nearly 50% in those older than 65 (24). At younger ages, microalbuminuria predominates while in older age reduced GFR is increasingly prevalent among cases with DKD. This finding could be explained by the trend in using medications that reduce albuminuria, such as glucose-lowering medications and RAAS inhibitors.

However, the phenotype of reduced GFR with normoalbuminuria has been increasingly recognized in type 2 DM. In population-based studies of diabetes in the United States and Australia, 36%-55% of individuals with reduced GFR did not have concurrent microalbuminuria or macroalbuminuria. Frequently, non-albuminuric reduced GFR was observed in the absence of diabetic retinopathy, suggesting underlying processes other than diabetic glomerulopathy. In the UKPDS, female gender, advanced age and insulin resistance were risk factors for reduced GFR but not microalbuminuria, while male gender, adiposity, hyperglycemia and dyslipidemia were risk factors for microalbuminuria but not reduced GFR (22). Higher blood pressure was a risk factor for both reduced GFR and microalbuminuria.
PROGRESSION OF KIDNEY DISEASE IN TYPE 2 DIABETES

The progression and regression of established DKD is highly variable in type 2 DM. In the UKPDS, evolution from microalbuminuria to macroalbuminuria occurred at a rate of 2.8% per year, and change from macroalbuminuria to elevated plasma creatinine or ESKD occurred at a rate of 2.3% per year (25). Similar to what happens with type 1 DM, loss of GFR can occur at any level of urine albumin excretion but tends to be more rapid with greater urine albumin excretion. At the diagnosis of type 2 DM, 7.3% of patients had microalbuminuria or worse, rising to 17.3% after 5 years, 24.9% after 10 years and 28.0% after 15 years (25).

HEALTH CONSEQUENCES OF DIABETIC KIDNEY DISEASE

The high mortality risk observed among people with both types 1 and 2 DM is largely confined to those with evidence for DKD because it is associated with a number of interrelated cardiovascular diseases, including micro- and macroangiopathies.

DIABETIC KIDNEY DISEASE IN DIFFERENT COUNTRIES

Diabetic nephropathy is more frequent in African Americans, Asian Americans, and native Americans (26). Progressive kidney disease is more frequent in Caucasian patients with type 1 than type 2 DM, although its overall prevalence in the diabetic population is higher in patients with type 2 DM because this type of DM is more prevalent (27). The occurrence of diabetic nephropathy in Pima Indians is very interesting, indeed. Craig et al. have reported that around 50% of Pima Indians with type 2 DM developed nephropathy after 20 years of the disease, and 15% of them were already in the terminal stage of kidney failure (28). In the United States, the occurrence of diabetic nephropathy in patients beginning kidney replacement therapy doubled in the late 1990s (28). Fortunately, the trend has been decreasing, most likely due to better prevention and earlier diagnosis and treatment of DM (29).

In the USA, 25.6 million adults (11.3%) aged 20 years and more had diabetes in 2011, with the prevalence increasing in older age groups (26.9% of people aged ≥65). However, nearly 3% of newly diagnosed patients with type 2 DM have overt nephropathy. Among people with diabetes, the prevalence of DKD remained stable (3). Approximately 44% of new patients entering dialysis in the United States are diabetics. Early diagnosis of diabetes and early intervention are critical in preventing normal progression to renal failure seen in many type 1 and a significant percentage of type 2 diabetics. The prevalence of diabetes is higher in certain racial and ethnic groups, affecting approximately 13% of African Americans, 9.5% of Hispanics, and 15% of native Americans, primarily with type 2 DM (30, 31). Nearly 20% to 30% of all diabetics will develop evidence of nephropathy, although a higher percentage of type 1 patients progress to ESKD.

Epidemiological differences are recorded among European countries, mainly Germany. The proportion of patients admitted for renal replacement therapy is higher than that reported from the United States. In Heidelberg (southwest of Germany), nearly 60% of patients admitted for renal replacement therapy in 1995 had diabetes, with the majority (90%) of type 2 DM. An increase in ESKD secondary to type 2 DM has been noted even in countries known to have low incidences of type 2 DM, such as Denmark and Australia. The exact incidence and prevalence in Asia are not currently available (3).

Pavkov et al. (32) report that diabetic nephropathy affects males and females equally, and it rarely develops before 10-year duration of type 1 DM. The role of age in the development of DKD is unclear although the mean age of patients who reach ESKD is about 60 years and the incidence of DKD is higher among elderly persons who have had type 2 diabetes for a longer time. In Pima Indians with type 2 DM, the earlier the onset of diabetes, the higher is the risk of progression to ESKD.
The incidence and severity of diabetic nephropathy are 3- to 6-fold higher in blacks than in whites. Similarly, diabetic nephropathy is more common among Mexican Americans and Pima Indians with type 2 DM. This suggests that socioeconomic factors such as diet, poor control of hyperglycemia, hypertension, and obesity have a primary role in the development of diabetic nephropathy. Familial clustering may be one of the important factors in these populations.

Bhalla et al. (33) report that in patients with type 2 DM, racial/ethnic minorities were more likely to have proteinuric DKD and less likely to have nonproteinuric DKD.

Diabetic nephropathy has become an important clinical and public health challenge, as reported by de Boer et al. (3), who estimated the disease burden in the US adult population aged 20 years or older using data from the National Health and Nutrition Examination Survey. In a cross sectional study including 32,208 type 2 DM patients from 33 countries, Parving et al. report on the prevalence of micro-/macroalbuminuria to be 38.8% and 9.8%, respectively (34). Asian and Hispanic patients had the highest prevalence of microalbuminuria (43.2% and 43.8%) and macroalbuminuria (12.3% and 10.3%), while Caucasians had the lowest microalbuminuria (33.3%) and macroalbuminuria (7.6%). Twenty-two percent of patients had compromised renal function (GFR <60 mL/min/1.73 m²). Unnikrishnan et al. (35) report that the prevalence of overt nephropathy and microalbuminuria was 2.2% and 26.9%, respectively, among type 2 diabetics in urban Asian Indians. Among 8,897 Japanese type 2 DM patients from 29 medical clinics or general/university-affiliated hospitals from different areas, the prevalence of microalbuminuria and decreased GFR (<60 mL/min/1.73 m²) was 31.6% and 10.5%, respectively (36).

In the US population, the Pathways Study-across-sectional analysis among 2,969 primary care diabetics of a large local health maintenance organization observed the racial/ethnic differences in early diabetic nephropathy despite comparable access to diabetes care. Among non-hypertensives, microalbuminuria was twofold greater (odds ratio 2.01; 95% confidence interval (CI) 1.14-3.53) and macroalbuminuria was threefold greater (odds ratio 3.17; 95% CI 1.09-9.26) for Asians compared with whites. Among hypertensive patients, adjusted odds of microalbuminuria were greater for Hispanics (odds ratio 3.82; 95% CI 1.16-12.57) than whites, whereas adjusted odds of macroalbuminuria were threefold greater for blacks (odds ratio 3.32; 95% CI 1.26-8.76) than for whites (37).

What is new is the recent unreasonable rise in the prevalence of metabolic syndrome (38) and of type 2 DM (39) worldwide, which is extremely pronounced in Asian countries (39), especially in India, the ‘diabetes capital of the world’ (40-43). Indian diabetics have a propensity to have insulin resistance, higher waist circumference despite lower body mass index, as well as lower adiponectin and higher inflammatory markers (43). The prevalence of overt diabetes is particularly high in Indian elderly (44), in addition to prediabetes and overt diabetes in the young (44, 45), and consequently diabetic nephropathy, especially in rural populations of India (46-50). The estimated overall incidence rate of chronic kidney disease and ESKD in India is currently 800 per million population and 150-200 per million population, respectively (50).

Of great interest is the fact that the risks of impaired fasting glucose and impaired glucose tolerance are markedly higher in citizens of a South-East Asian origin compared with the local populations of European origin (51). Furthermore, the prevalence of any type of chronic kidney disease and its rate of progression, and specifically also of diabetic nephropathy, is significantly higher in the citizens of Asian origin, as observed both in the UK (54) and Canada (53), presumably as the result of different genetics and/or lifestyle and the lack of awareness of kidney complications of diabetes (54).

As many as six Arabic-speaking countries are among the world’s leaders in terms of type 2 DM prevalence; these countries are Kuwait, Lebanon, Qatar, Saudi Arabia, Bahrain, and the United Arab Emirates (UAE). Rapid economic growth brings with it great opportunities for improvements in the infrastructure (e.g., health care and education), it also carries with it the burden of greater reliance on mechanization, a
proliferation of Western-style fast food, access to cheap migrant labor, and as elsewhere, greater opportunities for sedentary lifestyles, especially in the young (55).

In a cross-sectional study from Egypt, 42% of diabetics had nephropathy (56); in Jordan, 33% of diabetics at a national diabetes center had nephropathy (57); and at a diabetic clinic in Libya, 25% of patients had nephropathy (58).

GERIATRICS AND DIABETIC NEPHROPATHY

Increase in the prevalence of diabetic nephropathy also derives directly from the growth in the prevalence of diabetic nephropathy among individuals aged 65 years and older. Individuals older than 65 are unduly affected by diabetes and related ESKD. According to data from the National Health and Nutrition Examination Survey, diabetes prevalence was 26.9% among people aged ≥65 (59, 60). The prevalence of diabetic nephropathy increased from 7.1% in 1988-1994 to 8.6% in 1999-2004 and 10.7% in 2005-2008 among individuals aged 65 years and older (3, 61). Recent data also revealed that the adjusted point prevalence rates per million population of reported diabetes-related ESKD for individuals aged 60-69 and ≥70 were 410.3 and 475.7 in whites and 1439.9 and 1471.5 in Africans (62, 63).

One of the challenges of managing the elderly with diabetic nephropathy is that they may develop more complications, especially heart, eye, and peripheral vascular diseases. In their 2011 National Diabetes Fact Sheet, the Centers for Disease Control (CDC) reported that in 2004, heart disease and prior stroke were noted on 68% and 16% of diabetes-related death certificates, respectively, among people aged 65 years or older (59). Moreover, the CDC indicated that, in 2005, 27% of adults with diabetes aged ≥75 reported some degree of visual impairment compared with 15% of diabetic patients aged 18-44 (59). Individuals aged ≥65 account for 55% of diabetic subjects who had nontraumatic lower extremity amputations (64). Caring for elderly patients with diabetic renal disease imposes a huge financial burden on governments and family members. For example, the American Diabetes Association indicated that the total estimated cost of diabetes in 2007 was $174 billion, including $58 billion to treat diabetes-related chronic complications (65).

Diabetic nephropathy in the elderly is mainly due to type 2 DM and its distribution is uneven among racial groups. American-Indians, African-Americans, and Mexican-Americans have a greater incidence than Caucasians by as much as three to one depending on the minority cohort selected for comparison (63).

Nearly all studies demonstrating beneficial effects of metabolic and blood pressure controls on DKD have been performed in young to middle-aged cohorts. Importantly, the management of DKD in older people is frequently based on extrapolations of data gathered in selected and motivated younger people. Moreover, people older than 70 have been virtually excluded in trials supporting major US practice guidelines for the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in chronic kidney disease. In managing diabetes and diabetic nephropathy in the elderly, clinicians should keep in mind several key points:

1) elderly diabetic patients constitute a diverse group expressing various clinical and functional situations;
2) the American Geriatric Society Panel on Improving Care for Elders with Diabetes recommends that treatment of elderly patients with diabetes focus on specific problems and priorities (66);
3) the American Geriatric Society has also introduced the concept of time horizon for the benefits of certain treatments. Glycemic control may take as long as 8 years to have positive results on microvascular complications. Benefits of good blood pressure and lipid control may not be noticeable before 2 or 3 years (67);
4) many elderly patients with diabetes are fragile and are also at a greater risk of developing several common geriatric syndromes, such as depression, cognitive impairment, urinary incontinence, injurious falls, and persistent pain.

The Assessing Care of Vulnerable Elders...
(ACOVE) project defines a frail elderly patient as a vulnerable person who is older than 65 and is at an increased risk of death or functional decline within 2 years (67); 5) in consequence, renoprotection in a geriatric population should be tailored according to patient’s autonomy, degree of frailty, life expectancy, comorbidity index, and the stage of diabetic nephropathy; and 6) elderly diabetic patients may be susceptible to nephrotoxic agents such as radiocontrast; specific caution should be taken in preventing and monitoring radiocontrast induced nephropathy.

In conclusion, diabetic nephropathy is not an uncommon complication of diabetes (types 1 and 2) all over the world and among geriatric population.
REFERENCES


SUMMARY

This prospective study (September 2011–September 2012) including 250 patients investigated the controversial role of obesity indices in clinical severity and prognosis of acute ST-elevation myocardial infarction (STEMI) treated with primary percutaneous coronary intervention. Study patients were grouped according to obesity indices: body mass index (BMI) (<25.0, 25.0–29.9 and ≥30.0 kg/m²), waist circumference (WC) (<102/88 and ≥102/88 cm), waist-to-hip ratio (WHR) (<0.90/0.85 and ≥0.90/0.85) and waist-to-height ratio (WHtR) (<53/49, 53/49–62/57 and ≥63/58). The groups were analyzed by the baseline, severity (clinical, laboratory, echocardiography, coronary angiography, and in-hospital complications) and prognostic parameters (major adverse cardiovascular events, and sick leave during 12-month follow up). While BMI <25.0 kg/m² increased and BMI 25.0–29.9 kg/m² reduced the risk of dyspnea, WHR ≥0.90/0.85 increased the risk of significant proximal/middle coronary segment stenosis and WHtR ≥63/58 increased the risk of heart failure and total in-hospital complications (p<0.05). In conclusion, WHR and for the first time used WHtR are superior to BMI in predicting acute STEMI severity, while WC has no influence on it. Obesity indices have no impact on prognosis.

INTRODUCTION

Overweight and obesity are one of the major public health problems. Obesity prevalence in Europe has reached epidemic proportions (up to 28.3% of men and 36.5% of women) with higher prevalence rates in Central, Eastern, and Southern Europe than those in Western and Northern Europe (1,2). Obesity is an independent risk factor for the development of cardiovascular disease (CVD), including coronary artery disease (CAD) and heart failure. It is frequently
associated with arterial hypertension, diabetes mellitus type 2 and atherogenic dyslipidemia, as well as with an increased risk of all-cause morbidity and mortality (3).

Measurement of body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR) and waist-to-height ratio (WHtR) is a primary method for diagnosing obesity. While BMI determines overall obesity, other obesity indices are related to central obesity. Also, they are stronger predictors of CVD risk than BMI (4-6). It is not surprising because central obesity correlates with excessive visceral fat, which is directly associated with insulin resistance and compensatory hyperinsulinemia, dyslipidemia and inflammatory states that synergistically lead to smooth muscle cell proliferation, calcium and cholesterol ester deposition in the artery, and finally to atherosclerotic vascular disease (7-9).

In subjects with acute myocardial infarction (MI), there is a positive association of increasing abdominal obesity with higher mortality, as well as an inverse association between BMI and mortality (‘obesity paradox’). The possible explanation could be that BMI does not adequately discriminate the difference between body fat (especially abdominal) and lean muscle mass (5).

The main objectives of this study were to evaluate the severity and prognosis of acute ST-elevation myocardial infarction (STEMI) in patients with various obesity indices and treated with primary percutaneous coronary intervention (PCI). Also, for the first time, we investigated the involvement of coronary artery (CA) segments with significant stenosis, as well as sick leave duration (SLD) in these patients.

PATIENTS AND METHODS

We prospectively analyzed 250 consecutive patients with acute STEMI treated with primary PCI in Department of Cardiology, Sestre milosrdnice University Hospital Center (September 2011-2012). The inclusion criteria were presenting within 12 h from the onset of symptoms (history of chest pain/discomfort lasting for 10-20 minutes or more, not responding fully to nitroglycerine), persistent ST-segment elevation on electrocardiography (ECG) in at least two consecutive leads, or (presumed) new left bundle branch block (LBBB), and elevated cardiac laboratory biomarkers (cardiac troponin T (cTnT) and creatine kinase (CK)). The diagnosis of acute STEMI was established and primary PCI performed using the criteria of the European Society of Cardiology (10,11). The study was approved by the Ethics Committee of the Sestre milosrdnice University Hospital Center, Zagreb, Croatia.

After primary PCI, patients were grouped according to the obesity indices as follows: BMI (<25.0, 25.0-29.9 and ≥30.0 kg/m² for normal weight, overweight and overall obesity, respectively), WC (<102/88 and ≥102/88 cm for normal weight and central obesity in males/females, respectively), WHR (<0.90/0.85 and ≥0.90/0.85 for normal weight and central obesity in males/females, respectively) and WHtR (<53/49, 53/49-62/57 and ≥63/58 for normal weight, overweight and central obesity in males/females, respectively) (5,12-14).

The groups were analyzed by baseline, as well as severity and prognostic parameters of acute STEMI as follows:

Baseline demographic and medical history parameters included gender, age, arterial hypertension, dyslipidemia (elevated triglycerides and/or low HDL cholesterol), hyperglycemia, smoking status, known family history of cardiovascular events (MI, cerebrovascular insult), previous MI, previous PCI and coronary artery bypass grafting (CABG). For the diagnosis of dyslipidemia, hypertension and hyperglycemia, we used the criteria published by the National Cholesterol Education Program – Adult Treatment Panel III group (12), as follows:

Hypertriglyceridemia: triglycerides ≥150 mg/dL (1.7 mmol/L), or on medication for elevated triglycerides;

Low HDL-cholesterol: <40 mg/dL (1.04 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females, or on medication for low HDL-cholesterol;

Hypertension: blood pressure ≥130/85 mm Hg, or on medication for hypertension;
Hyperglycemia: fasting plasma glucose ≥100 mg/dL (5.6 mmol/L), or on medication for hyperglycemia;

The severity of acute STEMI was estimated by clinical presentation (angina pectoris, dyspnea, and duration of hospitalization), in-hospital complications (arrhythmias, conduction disturbances, reperfusion arrhythmias, heart failure, cardiogenic shock, cardiac arrest, mechanical ventilation, reinfarction, repeated PCI, mortality, and total in-hospital complications), coronary angiography, laboratory (maximal cTnT, CK) and echocardiography (left ventricular ejection fraction, LVEF) findings.

Coronary angiography was performed by applying a monoplane system (Axiom Artis, Siemens, Erlangen, Germany) by a common technique, as recommended in current guidelines (11). Patients received 70 IE/kg unfractionated heparin, 300 mg aspirin, a loading dose of 600 mg clopidogrel, and a GPIIb/IIIa inhibitor according to judgment of interventional cardiologist. CA stenosis of more than 50% was considered clinically significant. We analyzed the number of significantly narrowed CAs, number, length and diameter of stents used. Additionally, for the first time, we analyzed significantly stenosed segments of CAs. For that purpose, and according to the modified American Heart Association classification (15), CAs were divided into 16 segments. Segments were classified in two groups, as follows:

Proximal and middle CA segments: segment 1 (right coronary artery (RCA), proximal), segment 2 (RCA, mid), segment 5 (main stem), segment 6 (left anterior descending coronary artery (LAD), proximal), segment 7 (LAD, mid), segment 9 (first diagonal, D1), segment 11 (left circumflex artery (LCX), proximal), segment 12 (obtuse marginal, OM);

Distal CA segments: segment 3 (RCA, distal), segment 4 (right posterior descendens), segment 8 (LAD, distal), segment 10 (second diagonal, D2), segment 13 (LCX, distal), segment 14 (LCX, posterolateral branch), segment 15 (LCX, posterodescendens branch), segment 16 (RCA, posterolateral branch).

Serum CK activity was measured by spectrophotometry (Olympus 680, Beckman Coulter Inc., California, USA). Serum cTnT levels were measured by electrochemiluminescence (ECL) assay (Cobas e411, Roche Diagnostics, Sussex, UK). During hospital stay, echocardiography was performed in all patients (Acuson Sequoia 512, Siemens, Munich, Germany) according to the clinical standards and current echocardiography guidelines (16).

The prognosis of acute STEMI was estimated using MACE parameters (reinfarction, CA restenosis and new stenosis, cardiac and non-cardiac rehospitalization, CVI, urgent CABG, mortality, total MACE) during 12-month follow up. Data were collected by medical examination, checking medical documentation, or telephone contact with patients, family members or home physicians. In addition, during the same follow up period, we collected data on SLD of working population.

Statistical analysis

Qualitative data were expressed as absolute number and percentage. We used \( \chi^2 \)-test with Yates correction for comparison and analysis. Quantitative data were expressed as median and corresponding interquartile range. Differences between two groups were tested by Mann-Whitney U test. Differences among three groups were tested by nonparametric analysis of variance (Kruskal-Wallis ANOVA). Logistic regression analysis was used to investigate the relationship between one dependent and one or more independent variables that may influence or predict the value of the dependent variable. The level of statistical significance was set at \( p<0.05 \). Processing was done using the STATISTICA 6.0 for Windows software.

RESULTS

Among 250 patients, there were 72 (28.8%) patients with BMI ≥30.0 kg/m², 149 (59.6%) with WC ≥102/88 cm, 222 (88.8%) with WHR ≥0.90/0.85 and 81 (32.4%) with WHtR ≥63/58. We recorded the following results:
1) BMIs ≥30.0 kg/m² had the highest rates of hypertension (34 (56.7%) vs. 84 (71.2%) vs. 63 (87.5%), p=0.000) and dyslipidemia (40 (66.7%) vs. 88 (74.6%) vs. 62 (86.1%), p=0.030). Also, they had longest hospitalization and widest stents, while BMIs <25.0 kg/m² had the highest rates of dyspnea (Table 1).

2) WCs ≥102/88 cm were more frequently females (14 (13.9%) vs. 59 (39.6%), p=0.000) and had higher rates of hypertension (54 (53.5%) vs. 127 (85.2%), p=0.000). In comparison with WCs <102/88 cm, all parameters of severity and prognosis were without significant differences (Table 1).

3) WHRs ≥0.90/0.85 were more frequently males (8 (28.6%) vs. 169 (76.1%), p=0.000) and had higher rates of dyslipidemia (17 (60.7%) vs. 173 (77.9%), p=0.044). Also, they had higher rates of significantly stenosed proximal/middle CA segments (Table 2).

4) WHtRs ≥63/58 were more frequently females (10 (20%) vs. 18 (15.1%) vs. 45 (55.6%), p<0.0001) and had the highest rates of arterial hypertension (29 (58%) vs. 79 (66.4%) vs. 73 (90.1%), p<0.0001), heart failure and total in-hospital complications (p<0.05). Other baseline and parameters of severity, as well as all prognostic parameters were without significant differences (Table 2).

5) BMI <25.0 kg/m² increased (odds ratio (OR) 2.0, confidence interval (CI) [1.09-3.68], p=0.03) and BMI 25.0-29.9 kg/m² reduced the risk of dyspnea (OR 0.52, CI [0.30-0.91], p=0.02). WHtR ≥63/58 adjusted for hyperglycemia increased the risk of heart failure (OR 2.05, CI [1.13-3.71] p=0.02) and total in-hospital complications (OR 1.94, CI [1.13-3.33] p=0.02), while WHR ≥0.90/0.85 adjusted for gender increased the risk of proximal/middle CA segments stenosis (OR 3.34, CI [1.13-9.86], p=0.03). The number of significantly stenosed CAs, adjusted for LVEF and distal CA segment stenosis increased the risk of total MACE (OR 1.79, CI [1.17-2.77], p=0.01).

**DISCUSSION**

The main finding of this study was that WHR and WHtR proved superior to BMI in predicting clinical severity (significant proximal/middle CA segment stenosis, heart failure and total in-hospital complications vs. dyspnea), while WC had no influence on it. Obesity indices had no influence on prognosis. Finally, the number of significantly stenosed CAs increased the risk of total MACE, which is consistent with literature data (17).

Several studies have reported a paradoxical clinical effect of elevated BMI on improved survival after PCI in patients with acute STEMI, i.e. the overall ‘obesity paradox’ (18-21). Overweight and obese patients had wider stents, normal LVEF, lower CK levels, in-hospital and overall mortalities, as well as lower rates of MACE during 12-month follow up (22). Patients with normal BMI had more serious CA calcification, smallest vessel size, and thus a less favorable artery/device ratio; they had highest rates of in-hospital mortality and MACE 12 months after primary PCI (23-27). Other obese patients with acute STEMI had similar PCI characteristics and MACE as normal weight and overweight patients (28). Overweight and obesity did not result in significantly greater myocardial damage and left ventricular dysfunction, either in the acute phase or 6 months after acute MI treated with primary PCI (29). Iakobishvili et al. and Li et al. found no significant differences in infarct size, and in 3-month and 1-year outcomes among the BMI categories with acute STEMI and primary PCI (30,31). The ‘obesity paradox’ could explain why we found no significant differences among normal weight, overweight and overall obese patients in prognosis (MACE and SLD), as well as that of the severity parameters, normal weight increased and overweight reduced the risk of dyspnea.

The presence of increased WC is associated with greater myocardial necrosis and worsened LVEF in patients with acute MI (32,33). However, the protective role of increased WC in the presence of significant angiographic CAD, i.e. central ‘obesity paradox’ has been described (34). Subcutaneous fat component is probably mainly responsible for the
**Table 1. Severity and prognosis of acute ST-elevation myocardial infarction according to BMI (kg/m²) and WC (cm)**

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>BMI &lt;25.0 (n = 60)</th>
<th>BMI 25.0-29.9 (n = 118)</th>
<th>BMI ≥30.0 (n = 72)</th>
<th>p</th>
<th>WC &lt;102/88 (n = 101)</th>
<th>WC ≥102/88 (n = 149)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
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<tr>
<td>Angina pectoris, n (%)</td>
<td>60 (100)</td>
<td>114 (96.6)</td>
<td>71 (98.6)</td>
<td>0.283</td>
<td>99 (98)</td>
<td>146 (98)</td>
<td>0.985</td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td>25 (41.7)</td>
<td>27 (22.9)</td>
<td>23 (31.9)</td>
<td><strong>0.032</strong></td>
<td>27 (26.7)</td>
<td>48 (32.2)</td>
<td>0.353</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>9 (2-31)</td>
<td>8.5 (2-21)</td>
<td>9 (6-32)</td>
<td><strong>0.028</strong></td>
<td>8 (2-30)</td>
<td>9 (3-32)</td>
<td>0.126</td>
</tr>
<tr>
<td>In-hospital complications</td>
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<td></td>
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</tr>
<tr>
<td>Arrhythmias, n (%)</td>
<td>11 (18.3)</td>
<td>20 (17)</td>
<td>12 (16.7)</td>
<td>0.964</td>
<td>14 (13.9)</td>
<td>29 (19.5)</td>
<td>0.250</td>
</tr>
<tr>
<td>Conduction abnorm., n (%)</td>
<td>6 (10)</td>
<td>6 (5.1)</td>
<td>4 (5.6)</td>
<td>0.422</td>
<td>4 (4)</td>
<td>12 (8.1)</td>
<td>0.194</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>17 (28.3)</td>
<td>25 (21.2)</td>
<td>22 (30.6)</td>
<td>0.306</td>
<td>20 (19.8)</td>
<td>44 (29.5)</td>
<td>0.084</td>
</tr>
<tr>
<td>Cardiogenic shock, n (%)</td>
<td>6 (10)</td>
<td>8 (6.8)</td>
<td>4 (5.6)</td>
<td>0.598</td>
<td>7 (6.9)</td>
<td>11 (7.4)</td>
<td>0.892</td>
</tr>
<tr>
<td>Cardiac arrest, n (%)</td>
<td>9 (15)</td>
<td>16 (13.6)</td>
<td>11 (15.3)</td>
<td>0.937</td>
<td>12 (11.9)</td>
<td>24 (16.1)</td>
<td>0.350</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>2 (3.3)</td>
<td>5 (4.2)</td>
<td>3 (4.2)</td>
<td>0.955</td>
<td>2 (2)</td>
<td>8 (5.4)</td>
<td>0.180</td>
</tr>
<tr>
<td>Reinfarction, n (%)</td>
<td>0 (0)</td>
<td>1 (0.8)</td>
<td>0 (0)</td>
<td>-</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td>Re-PCI, n (%)</td>
<td>1 (1.7)</td>
<td>3 (2.5)</td>
<td>0 (0)</td>
<td>-</td>
<td>1 (1)</td>
<td>3 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>6 (10)</td>
<td>6 (5.1)</td>
<td>7 (9.7)</td>
<td>0.365</td>
<td>10 (9.9)</td>
<td>9 (8.3)</td>
<td>0.258</td>
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<tr>
<td>Total, n (%)</td>
<td>27 (45)</td>
<td>45 (38.1)</td>
<td>32 (44.4)</td>
<td>0.575</td>
<td>36 (35.6)</td>
<td>68 (45.6)</td>
<td>0.116</td>
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<tr>
<td>Laboratory</td>
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</tr>
<tr>
<td>Max. cTnT (ng/mL)</td>
<td>3.7 (0-10)</td>
<td>3 (0-10)</td>
<td>2.9 (0-10)</td>
<td>0.642</td>
<td>3.5 (0-10)</td>
<td>2.8 (0-10)</td>
<td>0.246</td>
</tr>
<tr>
<td>Max. CK (U/L)</td>
<td>1915.5 (107-15617)</td>
<td>1779 (25-13769)</td>
<td>1900 (85-14094)</td>
<td>0.952</td>
<td>2571 (70-15617)</td>
<td>1701 (25-14094)</td>
<td>0.296</td>
</tr>
<tr>
<td>ECHO</td>
<td>Left ventricle ejection fraction (%)</td>
<td>50 (28-70)</td>
<td>53 (25-70)</td>
<td>50 (30-76)</td>
<td>0.949</td>
<td>50 (25-64)</td>
<td>50 (28-76)</td>
</tr>
<tr>
<td>Coronary angiography</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Stenosed CAs, n (%)</td>
<td>2 (1-4)</td>
<td>2 (1-4)</td>
<td>1 (1-3)</td>
<td>0.456</td>
<td>1 (1-4)</td>
<td>2 (1-4)</td>
<td>0.399</td>
</tr>
<tr>
<td>≥2 stenosed CAs, n (%)</td>
<td>33 (55)</td>
<td>60 (50.8)</td>
<td>35 (48.6)</td>
<td>0.761</td>
<td>48 (47.5)</td>
<td>80 (53.7)</td>
<td>0.339</td>
</tr>
<tr>
<td>Number of stents</td>
<td>1 (1-4)</td>
<td>1 (1-3)</td>
<td>1 (1-3)</td>
<td>0.266</td>
<td>1 (1-4)</td>
<td>1 (1-3)</td>
<td>0.269</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3 (2.5-4)</td>
<td>3.5 (2.3-4)</td>
<td>3.5 (2.8-4)</td>
<td><strong>0.000</strong></td>
<td>3.2 (2-4)</td>
<td>3.5 (2.3-4)</td>
<td>0.184</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>18 (8-36)</td>
<td>20 (8-38)</td>
<td>20 (8-38)</td>
<td>0.099</td>
<td>18.5 (8-38)</td>
<td>20 (8-38)</td>
<td>0.060</td>
</tr>
<tr>
<td>Proximal/middle CAs segment stenosis, n (%)</td>
<td>54 (90)</td>
<td>106 (90.6)</td>
<td>66 (91.7)</td>
<td>0.944</td>
<td>88 (88)</td>
<td>138 (92.6)</td>
<td>0.217</td>
</tr>
<tr>
<td>Distal CAs segments stenosis, n (%)</td>
<td>27 (45)</td>
<td>47 (40.2)</td>
<td>23 (31.9)</td>
<td>0.289</td>
<td>38 (39.2)</td>
<td>59 (39.6)</td>
<td>0.800</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
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</tr>
<tr>
<td>Non-cardiac rehosp., n (%)</td>
<td>5 (9.4)</td>
<td>3 (2.8)</td>
<td>1 (1.5)</td>
<td>0.059</td>
<td>4 (4.4)</td>
<td>5 (3.7)</td>
<td>0.786</td>
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<tr>
<td>CVI, n (%)</td>
<td>1 (1.9)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
<td>0 (0)</td>
<td>1 (0.7)</td>
<td>-</td>
</tr>
<tr>
<td>Urgent CABG, n (%)</td>
<td>1 (1.9)</td>
<td>3 (2.8)</td>
<td>2 (2.9)</td>
<td>0.925</td>
<td>1 (1.1)</td>
<td>5 (3.7)</td>
<td>0.236</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>3 (5.7)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>-</td>
<td>2 (2.2)</td>
<td>2 (1.5)</td>
<td>-</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>11 (20.8)</td>
<td>20 (18.4)</td>
<td>16 (23.5)</td>
<td>0.706</td>
<td>18 (19.8)</td>
<td>29 (20.9)</td>
<td>0.842</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick leave duration (weeks)</td>
<td>12 (2-52)</td>
<td>12 (1-28)</td>
<td>14 (2-48)</td>
<td>0.401</td>
<td>12 (1-48)</td>
<td>12 (3-52)</td>
<td>0.093</td>
</tr>
</tbody>
</table>

BMI = body mass index; CABG = coronary artery bypass graft; CAs = coronary arteries; CK = creatinine phosphokinase; cTnT = cardiac troponin T; CVI = cerebrovascular insult; ECHO = echocardiography; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention; WC = waist circumference.
Table 2. Severity and prognosis of acute ST-elevation myocardial infarction according to WHtR (kg/m²) and WHR

<table>
<thead>
<tr>
<th>PARAMETERS</th>
<th>WHtR &lt;53/49 (n = 42)</th>
<th>WHtR 53/49-62/57 (n = 127)</th>
<th>WHtR ≥63/58 (n = 81)</th>
<th>p</th>
<th>WHR &lt;0.90/0.85 (n = 28)</th>
<th>WHR ≥0.90/0.85 (n = 222)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical presentation</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Angina pectoris, n (%)</td>
<td>41 (97.6)</td>
<td>124 (97.6)</td>
<td>80 (98.8)</td>
<td>0.836</td>
<td>27 (96.4)</td>
<td>218 (98.2)</td>
<td>0.529</td>
</tr>
<tr>
<td>Dyspnea, n (%)</td>
<td>15 (35.7)</td>
<td>36 (28.3)</td>
<td>24 (29.6)</td>
<td>0.662</td>
<td>10 (35.7)</td>
<td>65 (29.3)</td>
<td>0.484</td>
</tr>
<tr>
<td>Hospitalization (days)</td>
<td>8 (1-20)</td>
<td>9 (1-32)</td>
<td>9 (3-30)</td>
<td>0.366</td>
<td>9 (5-25)</td>
<td>9 (2-32)</td>
<td>0.193</td>
</tr>
<tr>
<td>In-hospital complications</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arrhythmias, n (%)</td>
<td>5 (11.9)</td>
<td>23 (18.1)</td>
<td>15 (18.5)</td>
<td>0.607</td>
<td>2 (7.1)</td>
<td>41 (18.5)</td>
<td>0.135</td>
</tr>
<tr>
<td>Conduction abnorm., n (%)</td>
<td>2 (4.8)</td>
<td>10 (7.9)</td>
<td>4 (4.9)</td>
<td>0.626</td>
<td>3 (10.7)</td>
<td>13 (5.9)</td>
<td>0.322</td>
</tr>
<tr>
<td>Heart failure, n (%)</td>
<td>9 (21.4)</td>
<td>26 (20.5)</td>
<td>29 (35.8)</td>
<td>0.038</td>
<td>9 (32.1)</td>
<td>55 (24.8)</td>
<td>0.400</td>
</tr>
<tr>
<td>Cardiogenic shock, n (%)</td>
<td>4 (9.5)</td>
<td>7 (5.5)</td>
<td>7 (8.6)</td>
<td>0.567</td>
<td>1 (3.6)</td>
<td>17 (7.7)</td>
<td>0.431</td>
</tr>
<tr>
<td>Cardiac arrest, n (%)</td>
<td>5 (11.9)</td>
<td>17 (13.4)</td>
<td>14 (17.3)</td>
<td>0.649</td>
<td>2 (7.1)</td>
<td>34 (15.3)</td>
<td>0.246</td>
</tr>
<tr>
<td>Mechanical ventilation, n (%)</td>
<td>1 (2.4)</td>
<td>4 (3.1)</td>
<td>5 (6.2)</td>
<td>0.467</td>
<td>0 (0)</td>
<td>10 (4.5)</td>
<td>0.252</td>
</tr>
<tr>
<td>Reinfarction, n (%)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (1.2)</td>
<td>-</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>Re-PCI, n (%)</td>
<td>0 (0)</td>
<td>4 (3.1)</td>
<td>0 (0)</td>
<td>-</td>
<td>0 (0)</td>
<td>4 (1.8)</td>
<td>-</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>5 (11.9)</td>
<td>9 (7.1)</td>
<td>5 (6.2)</td>
<td>0.499</td>
<td>2 (7.1)</td>
<td>17 (7.7)</td>
<td>0.923</td>
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<tr>
<td>Total, n (%)</td>
<td>12 (28.6)</td>
<td>49 (38.6)</td>
<td>43 (53.1)</td>
<td>0.020</td>
<td>10 (35.7)</td>
<td>94 (42.3)</td>
<td>0.503</td>
</tr>
<tr>
<td>Laboratory</td>
<td></td>
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</tr>
<tr>
<td>Max. cTnT (ng/mL)</td>
<td>3.7 (0.1-10)</td>
<td>3.7 (0-10)</td>
<td>2.6 (0-10)</td>
<td>0.061</td>
<td>2.1 (0-10)</td>
<td>3.2 (0-10)</td>
<td>0.071</td>
</tr>
<tr>
<td>Max. CK (U/L)</td>
<td>2652 (107-15617)</td>
<td>1983 (25-13331)</td>
<td>1420 (85-14094)</td>
<td>0.118</td>
<td>1324 (85-11425)</td>
<td>1926 (25-15617)</td>
<td>0.122</td>
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<tr>
<td>ECHO</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Left ventricle ejection fraction (%)</td>
<td>50 (25-65)</td>
<td>50 (28-76)</td>
<td>55 (30-68)</td>
<td>0.691</td>
<td>50 (30-70)</td>
<td>50 (25-76)</td>
<td>0.944</td>
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<td>Coronary angiography</td>
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</tr>
<tr>
<td>Stenosed CAs, n (%)</td>
<td>1.5 (1-3)</td>
<td>1 (1-4)</td>
<td>2 (1-4)</td>
<td>0.740</td>
<td>1.5 (1-4)</td>
<td>2 (1-4)</td>
<td>0.750</td>
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<tr>
<td>≥2 stenosed CAs, n (%)</td>
<td>21 (50.0)</td>
<td>62 (48.8)</td>
<td>45 (55.6)</td>
<td>0.629</td>
<td>14 (50)</td>
<td>114 (51.4)</td>
<td>0.893</td>
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<tr>
<td>Number of stents</td>
<td>1 (1-3)</td>
<td>1 (1-4)</td>
<td>1 (1-3)</td>
<td>0.432</td>
<td>1 (1-3)</td>
<td>1 (1-4)</td>
<td>0.119</td>
</tr>
<tr>
<td>Stent diameter (mm)</td>
<td>3 (2.8-4.0)</td>
<td>3.5 (2.5-4.0)</td>
<td>3.5 (2.3-4.0)</td>
<td>0.062</td>
<td>3 (2.8-4.0)</td>
<td>3.5 (2.3-4.0)</td>
<td>0.515</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>20 (8-36)</td>
<td>20 (12-38)</td>
<td>20 (12-36)</td>
<td>0.291</td>
<td>20 (8-36)</td>
<td>20 (8-36)</td>
<td>0.905</td>
</tr>
<tr>
<td>Proximal/middle CAs segment stenosis, n (%)</td>
<td>37 (88.1)</td>
<td>113 (89.7)</td>
<td>76 (93.8)</td>
<td>0.487</td>
<td>21 (75)</td>
<td>205 (92.8)</td>
<td>0.002</td>
</tr>
<tr>
<td>Distal CAs segments stenosis, n (%)</td>
<td>15 (35.7)</td>
<td>51 (40.5)</td>
<td>31 (38.3)</td>
<td>0.850</td>
<td>15 (53.6)</td>
<td>82 (37.1)</td>
<td>0.092</td>
</tr>
<tr>
<td>MACE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiac rehosp., n (%)</td>
<td>1 (2.7)</td>
<td>6 (5.1)</td>
<td>2 (2.6)</td>
<td>0.626</td>
<td>1 (3.7)</td>
<td>8 (4)</td>
<td>0.941</td>
</tr>
<tr>
<td>CVI, n (%)</td>
<td>0 (0)</td>
<td>1 (0.9)</td>
<td>0 (0)</td>
<td>-</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
<td>-</td>
</tr>
<tr>
<td>Urgent CABG, n (%)</td>
<td>0 (0)</td>
<td>4 (3.4)</td>
<td>2 (2.6)</td>
<td>-</td>
<td>0 (0)</td>
<td>6 (3)</td>
<td>-</td>
</tr>
<tr>
<td>Mortality, n (%)</td>
<td>0 (0)</td>
<td>3 (2.6)</td>
<td>1 (1.3)</td>
<td>-</td>
<td>0 (0)</td>
<td>4 (2)</td>
<td>-</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>5 (13.5)</td>
<td>28 (23.9)</td>
<td>14 (18.4)</td>
<td>0.340</td>
<td>7 (25.9)</td>
<td>40 (19.7)</td>
<td>0.451</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sick leave duration (weeks)</td>
<td>16 (2-24)</td>
<td>12 (1-52)</td>
<td>12 (3-40)</td>
<td>0.118</td>
<td>12 (10-26)</td>
<td>12 (1-52)</td>
<td>0.656</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass graft; CAs = coronary arteries; CK = creatinine phosphokinase; cTnT = cardiac troponin T; CVI = cerebrovascular insult; ECHO = echocardiography; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention; WHR = waist-to-hip ratio; WHtR = waist-to-height ratio
paradoxical protective effect of central obesity, whereas visceral fat may have an opposing effect and increase the risk of angiographic CAD. WC does not add prognostic information for predicting six-month mortality or myocardial reinfarction in patients with acute MI (35). Other authors have reported that WC is not associated with an increased incidence of MACE during 30-day follow up in patients with acute coronary syndrome (36). We found no significant differences in any of the parameters of severity and prognosis between patients with normal and increased WC.

The waist-to-hip ratio may indicate better distribution of body fat (37). The presence of increased WHR is associated with significant CA stenosis, but not with the number of significantly stenosed CAs (38). In acute STEMI, patients with WHR ≥0.90/0.85 more frequently have heart failure and WHR is an independent predictor of six-month mortality (39). In our study, where a small number of patients with normal WHR was found as expected, the presence of increased WHR was associated with significant stenosis of proximal/middle CA segments, but without significant differences in other severity and in all prognostic parameters.

Of the obesity indices, WHtR had the highest positive correlation with CAD (40). This was the first study on the effect of WHtR on clinical severity and prognosis of acute STEMI. We found that WHtR ≥63/58 increased the risk of heart failure and total in-hospital complications. Considering the small number of patients with normal WHR and WHtR values as the main limitation of this study, investigation with a higher number of patients should be performed to confirm these results.

In conclusion, WHR and for the first time used WHtR are superior to BMI in predicting acute STEMI severity, while WC has no influence on it. Obesity indices have no impact on the prognosis (MACE, SLD) of STEMI.
REFERENCES


SUMMARY

Glucagon-like peptide-1 (GLP-1) agonists are increasingly used in the management of type 2 diabetes (T2DM), but their long-term cardiovascular safety is not yet confirmed. In long-term clinical trials, therapy with GLP-1 receptor agonists has been associated with improvements in blood pressure but also with increases in heart rate (HR). In the present study, we assessed the effects of GLP-1 receptor agonists exenatide and liraglutide on systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR in overweight T2DM patients. A total of 85 overweight T2DM patients were included in the study (43 on exenatide and 42 on liraglutide) and followed up for 13 and 22 months. Treatment with exenatide caused a significant decrease in SBP from $146\pm20$ to $140\pm15$ mm Hg ($p=0.03$), while DBP (from $88\pm10$ to $85\pm7$ mm Hg ($p=0.1$)) and HR (from $78\pm10$ to $78\pm12$ beats/min ($p=0.9$)) did not change significantly. Treatment with liraglutide caused a significant decrease in SBP from $145\pm20$ to $135\pm18$ mm Hg ($p=0.005$) and DBP from $88\pm8$ to $82\pm8$ mm Hg ($p<0.001$), while HR (from $78\pm14$ to $73\pm8$ beats/min ($p=0.2$)) did not change significantly. The results of our study suggest that therapy with GLP-1 receptor agonists exenatide and liraglutide may significantly reduce SBP and DBP by 6 to 10 mm Hg.

INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists represent a novel class of therapies for type 2 diabetes (T2DM) treatment with a potent blood glucose-lowering action mediated via their ability to induce insulin secretion and reduce glucagon secretion in a glucose-dependent manner, but they also increase pancreatic β cell mass, and suppress appetite and delay in gastric emptying resulting in weight loss (1). These medications primarily lower prandial and fasting blood glucose levels by enhanced GLP-1 receptor signaling. They lower blood glucose without fear from hypoglycemia and preserve first-phase insulin
secretion. They are tailored to resist hydrolysis by DPP-4 activity and to provide longer durability in the circulation compared with native GLP-1 (1). Although intestinal GLP-1 secretion is triggered by a diverse variety of factors (metformin, interleukin-6, bile acids, and so forth), the classical view is that GLP-1 is secreted in the gut in response to nutrient ingestion as part of the enteroinsular axis (2). They are also efficient in reducing weight by slowing gastric emptying rate and reducing appetite (3). GLP-1 receptor agonists are synthetic analogues of human GLP-1 or exendin-4 based molecules. Exenatide, originally derived from salivary glands of the Gila monster with 53% homology with human GLP-1, was the first GLP-1 receptor agonist introduced in clinical practice. The once-daily human GLP-1 receptor agonist liraglutide has 97% homology with human GLP-1 with a single amino acid substitution extending its half-life to up to 13 hours (4). In clinical trials, exenatide and liraglutide significantly reduce HbA1c up to 1.5% when used either as monotherapy or as an add-on in combination with other oral hypoglycemic agents and insulin (5). Favorable outcomes have also been observed in systolic blood pressure (BP) reduction, postprandial intestinal lipoprotein metabolism, endothelial cell function, nonalcoholic fatty liver disease, modulation of innate immune-mediated inflammation and surrogate markers of renal function (6, 7). However, small increases in heart rate (HR) in long-term clinical trials with GLP-1 receptor agonists have also been observed. As hypertension and HR is an independent risk factor for premature death in patients with T2DM, the potential extrapancreatic effects, particularly within the heart and blood vessels, of this drug class are of considerable clinical interest (8). In the present study, we assessed the effects of liraglutide and exenatide on systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR in overweight T2DM patients.

SUBJECTS, MATERIALS AND METHODS

A total of 43 overweight T2DM patients on exenatide were included and followed-up for 22 months (age 57±7 years, 22M/21F, body mass index (BMI) 38±5 kg/m², weight 114±18 kg, HbA1c 8.6±1.2%, duration of diabetes 11±6 years). Forty-two patients (18 male and 24 female) on liraglutide were included in this study too. They were followed up for 13 months (age 58±7 years, 18M/24F, BMI 38±5 kg/m², weight 111±21 kg, HbA1c 8.1±0.9%, duration of diabetes 13±6 years). All subjects were studied in the morning after an overnight fast. Basic anthropometric measurements were performed on all study subjects, including BMI and waist circumference (WC). Fasting venous blood samples were collected in the morning between 08:00 and 09:30 AM after an overnight fast for determination of HbA1c. HbA1c was measured spectrophotometrically by turbidimetric immunoinhibition (Olympus AU600, Beckman-Coulter, USA). Results of HbA1c (%) are expressed in the DCCT-equivalent. Blood pressure was measured twice in the sitting position with a mercury sphygmomanometer after a resting period of 10 minutes. HR was determined using a standard 12-lead ECG after a resting period of 10 minutes. Data on serum creatinine levels, age, sex and race were used to calculate the estimated glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (9). Exenatide was started as a 5-µg twice daily dose and increased to 10 µg twice daily if needed in patients with estimated GFR ≥60 mL/min⁻¹/1.73 m². Liraglutide was started as a 0.6-mg once daily dose and increased to up to 1.8 mg.

The study protocol complied with the Declaration of Helsinki, as well as with local institutional guidelines, and was approved by the local ethics committees. Data are expressed as means ± SD for normally distributed values, as median with range for non-normally distributed values, and percentage. Differences between groups were examined, depending on the nature of the data, by parametric (t-test) or nonparametric (Mann-Whitney) tests. Statistical analysis was performed by statistical package STATA/IC ver. 11.1.
RESULTS

At the end of 22 months, 43 patients treated with exenatide had significantly decreased HbA1c from 8.6±1.2 to 8.0±1.3% (p=0.01), BMI from 38±5 to 36±5 kg/m² (p<0.001), weight from 114±18 to 106±18 kg (p<0.001), and WC from 119±12 to 115±11 cm (p<0.001). The 22-month administration of exenatide also caused a significant decrease in SBP from 146±20 to 140±15 mm Hg (p=0.03), while DBP (from 88±10 to 85±7 mm Hg (p=0.1)) and HR (from 78±10 to 78±12 beats/min (p=0.9)) did not change significantly (Table 1).

Treatment with liraglutide caused a significant decrease in BMI from 38±5 to 36±6 kg/m² (p<0.001), weight from 111±21 to 106±23 kg (p<0.001), and WC from 120±14 to 114±15 cm (p=0.006), while HbA1c (from 8.1±0.9 to 8.0±1.3% (p=0.1)) did not change significantly. However, the 13-month administration of liraglutide caused a significant decrease in SBP from 145±20 to 135±18 mm Hg (p=0.005) and DBP from 88±8 to 82±8 mm Hg (p<0.001), while HR (from 78±14 to 73±8 beats/min (p=0.2)) did not change significantly (Table 2).

Table 1. Baseline and end-of-study characteristics of patients treated with exenatide

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of study</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>57±7</td>
<td></td>
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<tr>
<td>Gender (M/F)</td>
<td>22/21</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>11±6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>119±12</td>
<td>115±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>38±5</td>
<td>36±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>114±18</td>
<td>106±18</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.6±1.2</td>
<td>8.0±1.3</td>
<td>0.01</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>146±20</td>
<td>140±15</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>88±10</td>
<td>85±7</td>
<td>0.1</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78±10</td>
<td>78±12</td>
<td>0.9</td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73 m²)</td>
<td>89±18</td>
<td>90±17</td>
<td>0.2</td>
</tr>
</tbody>
</table>

BP, blood pressure; GFR, glomerular filtration rate

Table 2. Baseline and end-of-study characteristics of patients treated with liraglutide

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>End of study</th>
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</tr>
</thead>
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<tr>
<td>Age (years)</td>
<td>58±7</td>
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<td></td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>18/24</td>
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<tr>
<td>Diabetes duration (years)</td>
<td>13±6</td>
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<tr>
<td>Waist circumference (cm)</td>
<td>120±14</td>
<td>114±15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>38±5</td>
<td>36±5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>111±21</td>
<td>106±23</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.1±0.9</td>
<td>8.0±1.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>145±20</td>
<td>135±18</td>
<td>0.005</td>
</tr>
<tr>
<td>Diastolic BP (mm Hg)</td>
<td>88±10</td>
<td>82±8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>78±14</td>
<td>73±8</td>
<td>0.2</td>
</tr>
<tr>
<td>Estimated GFR (mL/min/1.73 m²)</td>
<td>90±13</td>
<td>88±18</td>
<td>0.3</td>
</tr>
</tbody>
</table>

BP, blood pressure; GFR, glomerular filtration rate
DISCUSSION

Incretin-based medications are a newer class of diabetes therapies that are used worldwide for the treatment of T2DM. They have excellent therapeutic benefit in terms of HbA1c decline and weight reduction as manifested by BMI decrease, which we also confirmed in our study. Besides that, GLP-1 receptor agonists have other favorable effects on the cardiovascular system and the endovasculature, including BP reduction, which may be particularly advantageous in the treatment of T2DM. The results of our study suggest that therapy with the GLP-1 receptor agonists liraglutide and exenatide may significantly reduce SBP and DBP by 6 to 10 mm Hg and may offer an alternative therapy for overweight T2DM. Moreover, in our study, therapy with liraglutide and exenatide was not associated with an increase in HR.

Consistent but modest SBP reductions ranging from 2.1 to 6.7 mm Hg for liraglutide were observed in the Liraglutide Effect and Action in Diabetes (LEAD) trials (10). Office SBP reductions are routinely observed in clinical studies of 12-, 24- and 52-week duration with GLP-1R agonist therapy. Detailed office BP data from the LEAD studies demonstrated that treatment with liraglutide (in doses of 1.2 mg and 1.8 mg) significantly reduced SBP early after introduction (at 2 weeks, peaking at 4 weeks), preceding reductions in body weight (11). A recent extensive systematic meta-analysis and meta-regression by Katout et al. (12) of GLP-1 receptor agonist in 12,469 patients demonstrated that a greater reduction in SBP was achieved with GLP-1 receptor agonists than with active comparator therapy (2.97 vs. 1.47 mm Hg). As expected, the SBP-lowering effect was associated with a small increase in HR (0.26 vs. 2.33 beats/min). These results are in keeping with another recent meta-analysis by Robinson et al. (13), who demonstrated that GLP-1 receptor agonist administration was associated with a reduction in SBP by 1.79 mm Hg (2.94 to 0.64 mm Hg) vs. placebo and 2.39 mm Hg (3.35 to 1.42 mm Hg) vs. active control. A small increase in HR of 1.86 beats/min was also observed.

A variety of mechanisms may contribute to the antihypertensive effect(s) of GLP-1 receptor agonists. The possible mechanisms include non-renal mediated effects (weight loss, central inhibition of salt intake, inhibition of intestinal salt absorption, neurally stimulated catecholaminergic activity, endothelial-dependent vasodilatation) and renal-mediated effects (natriuresis, renal Na+/H+ ion exchange activity, renal hemodynamics (increased urinary flow/diuresis)) (14).

One unifying hypothesis that may partially account for the antihypertensive effect(s) of GLP-1 receptor agonists in humans is through the stimulation of natriuresis. A small series of preclinical and clinical studies have demonstrated that urinary sodium excretion is triggered in response to short-term infusion of GLP-17-36 amide and volume expansion by hypertonic saline infusion. Gutzwiller et al. (15) observed significant, dose-dependent increases in urinary sodium excretion in healthy subjects, and in obese, insulin-resistant subjects urinary sodium excretion increased by 60% vs. placebo in response to native GLP-1 infusion. This effect was observed in parallel with increased chloride ion and calcium ion filtration, suggesting a GLP-1-inhibitory effect at the level of the proximal tubule. Additionally, urine volume was also increased in response to GLP-17-36 amide infusion.

Skov et al. (16) have recently reported a reduction in systemic levels of the potent vasoconstrictor angiotensin II with acute GLP-1 infusion; however, urinary angiotensinogen expression (a biomarker of renal tissue RAAS activity) was unchanged in this same study, suggesting that the effect of GLP-1 on tissue intrarenal RAAS activity is unclear. More recently, a novel link between BP reduction and cardiac atrial natriuretic peptide (ANP) secretion in response to GLP-1 receptor activation via liraglutide was demonstrated in rodents rendered hypertensive by angiotensin II infusion (17). Although previously unrecognized, Kim et al. (17) importantly localized GLP-1 receptor expression in the cardiac atrium but, interestingly, not to the ventricles (where the majority of the cardioprotective effect of GLP-1 receptor agonists are thought to be targeted). In support to that study, a small study involving Chinese patients with
T2DM and prehypertension showed significant increases in ANP levels after 12 weeks of liraglutide administration. At present, there are mixed data supporting the relevance of a potential ANP-mediated gut-heart-renal axis for GLP-1 receptor agonist-dependent reductions in BP in humans.

In conclusion, a modest but significant lowering effect on BP with GLP-1 receptor agonists has been observed. A variety of mechanisms may contribute to the antihypertensive effect(s) of GLP-1 receptor agonists with natriuresis as the most important BP lowering mechanism. In our study, therapy with the GLP-1 receptor agonists liraglutide and exenatide significantly reduced SBP and DBP by 6 to 10 mm Hg, suggesting that GLP-1 receptor agonists may offer an alternative antihypertensive therapy for overweight T2DM patients.

REFERENCES


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