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Prediabetes in hypertensive patients: a common and dangerous co-morbidity

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ABSTRACT

Hypertension and diabetes are common medical disorders, and frequently co-exist. Both conditions increase cardiovascular events. Recent studies have recognized that non-diabetic dysglycemia, or prediabetes, is more prevalent than diabetes. Prediabetic dysglycemia may be present in many patients for several years prior to the development of overt diabetes. Like diabetes, it increases the risk for cardiovascular events. The association of hypertension with prediabetes is therefore not benign. Aggressive life style changes and targeted treatment of both conditions is mandatory to reduce the higher cardiovascular morbidity and mortality seen in these patients.

Keywords: hypertension, cardiovascular disease, prediabetes, diabetes mellitus, dyslipidemia, dysglycemia

Abbreviations: AACE : American Association of Clinical Endocrinologists; ACE: Angiotensin-converting-enzyme inhibitor; ARB: Angiotensin receptor blocker; ASH: American Society of Hypertension; AHA: American Heart Association; ADA: American Diabetic Association; CDC: Centers for Disease Control; CV: Cardiovascular; HbA1c: Glycosylated hemoglobin; HDL: High density lipoprotein ; HTN: Hypertension; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; JNC: Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LDL: Low density lipoprotein; TZD: Thiazolidinediones

1. INTRODUCTION

Diabetes mellitus is a worldwide epidemic disease (Wild et al. 2004), with a considerable drain on healthcare and financial resources (Hogan et al, 2003). It is also common in patients with hypertension, and further increases their morbidity and mortality. The majority of the diabetic patients suffer from type 2 diabetes mellitus. (ADA,2010) The progression to overt diabetes occurs over several years – with increasing insulin resistance and declining insulin secretion resulting in a gradual increase in fasting and postprandial glucose levels. This pre-diabetic dysglycemic stage is called prediabetes (Alan et al, 2013). It is estimated that 418 million people worldwide will suffer from prediabetes by the year 2025 (IDF, 2013) A large majority of prediabetic patients will advance to overt diabetes (Wilson et al, 2005). Unfortunately prediabetic patients also exhibit an increased propensity to develop premature adverse cardiovascular events, long before they progress to overt diabetes (Haffner et al, 2000). Evidence suggests a cardiovascular benefit with early intervention in these patients (Knowler et al, 2002). Hypertension, a common medical condition (Hajjar et al, 2006), is a well known risk factor for adverse cardiovascular events, including strokes, ischemic heart disease and heart failure (Williams, 2009). Clinical trials have shown that treating hypertension reduces the risk of these events (SHEP, 1991; VACSG. 1972, MRC, 1985) and decreases cardiovascular mortality. The combined presence of prediabetes and hypertension therefore further increases the risk of deleterious cardiovascular outcomes. The presence and management of prediabetes in patients with hypertension has however not been well studied. This clinical retrospective study evaluates their combined prevalence and briefly reviews the treatment options available in these patients.

2. METHODS

We reviewed 277 consecutive charts of hypertensive office patients who had their Hba1c recorded. Standard blood pressure measurement techniques were used with an appropriate-sized cuff at the level of the right atrium, with the patient rested for 5 minutes, and with the back supported. Systolic blood pressure was categorized as follows: Normal: less than 120/80 mmHg; Pre-HTN: 120 to 139/80 to 89 mmHg; HTN: 140/90 mmHg or greater: Stage 1: 140 to 159/90 to 99 mmHg, Stage 2: 160/100 mmHg or greater. All patients had been diagnosed with hypertension with at least 2 consecutive elevated BP measurements (≥140 mm Hg systolic and/or 90 mm Hg diastolic or ≥130/80 mm Hg in the presence of diabetes mellitus or chronic kidney disease). All patients were on lifestyle changes recommendations and conventional anti-hypertensive patients, consistent with JNC 7 (Chobanian et al, 2003) and ASH guidelines (Gradman et al, 2010). According to the criteria established by the American Diabetic Association, diabetes mellitus was diagnosed if symptoms of diabetes (polyuria, polydipsia, and unexplained weight loss) were associated with a casual plasma glucose concentration of 200 mg/dl (11.1 mmol) or more; a fasting glucose is more than 125 mg/dL, or 200 mg/dL or more at two hours after an oral 75-g glucose tolerance test, or hemoglobin A1c of 6.5% or higher. ADA's criteria for prediabetes include a fasting glucose of 100-125 mg/dL, or 140-199 mg/dL at two hours after an oral 75-g glucose tolerance test, or hemoglobin A1c of 5.7%-6.4%. In this study, diabetes mellitus was diagnosed if the HbA1c was 6.5% or higher. Known diabetics under dysglycemic treatment were labeled as diabetics, irrespective of the HbA1c levels. Prediabetes was diagnosed only if the HbA1c was 5.7% - 6.4% (39 - 46 mmol/mol without being on any anti-diabetic agents. No dysglycemia was diagnosed if HbA1c was at or less than 5.6 and the patients were not on any dysglycemic agents.

3. RESULTS

Of the 277 hypertensive patients there were 158 males and 119 females. Their ages ranged from 16 years to 92 years. Of the 158 patients, 76 (27%) had HbA1c <5.6. Of these there were 52 (69%) males and 24 (71%) females. 127 (46%) patients had had HbA1c between 5.7- 6.4. Of these there were 73 (57%) males and 54 (43%) females. 74 (27%) had HbA1c >6.5 or were known diabetics on treatment. Of these there were 33 (45%) males and 41 (55%) females (Fig.1).

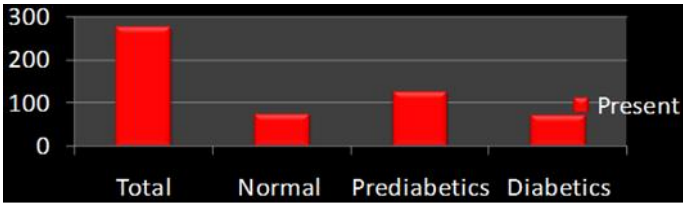

Figure 1
Results from 277 hypertensive patients

4. DISCUSSION

4.1. Diabetes

The human population is experiencing an inexorable rise in diabetes (Wild et al, 2004). It is estimated that the prevalence of diabetes worldwide will increase from 285 million in 2010 to 438 million in the year 2030 (CDC, 2010). Diabetes mellitus is associated with significant morbidity and premature mortality (Matsushima et al, 1997), mainly due to an increase in major cardiovascular events (Kannel et al, 1979). These include macrovascular complications such as coronary heart disease, (Huxley et al, 2006) cerbrovascular disease (Stegmayr et al, 1995) peripheral neuropathy (ADA, 2003) and microvascular complications, such as nephropathy (Adler et al, 2003) retinopathy (Harding, 2003) and neuropathy, which includes both autonomic (Vinik et al, 2001) and peripheral neuropathy (Veves et al, 2008).

4.2. Prediabetes

Prediabetes refers to dysglycemia that is not abnormal enough to be classified as diabetes. Prediabetes is very common in the USA (Cowie et al, 2009) and affects nearly 79 million Americans. Prevalence of prediabetes is increasing worldwide and experts have projected that more than 470 million people will have prediabetes by the year 2030. Prediabetes raises short-term absolute risk of type 2 diabetes by 3-to 10-fold, with some populations exhibiting greater risk than others (Tabak et al, 2012). Prediabetes is also associated with a moderate increase in cardiovascular risk (Unwin et al, 2002; Levitan et al, 2004). Most patients with prediabetes have the same CV risk factors as patients with type 2 diabetes, including dyslipidemia, hypertension, obesity, physical inactivity, insulin resistance, a procoagulant state, endothelial dysfunction and inflammation (David et al, 2007). This places these patients at a higher risk for macrovascular complications such as myocardial infarctions and stroke (Danaei et al, 2006; Vermeer et al, 2006) and microvascular complications such as nephropathy, chronic kidney disease, small fibre neuropathy, and diabetic retinopathy (Dunstan et al, 2004). Prediabetes is also associated with increased all-cause mortality (Nakagami et al, 2004; Wen et al, 2005).

4.3. Early Intervention in Prediabetes

The high prevalence of prediabetes in our hypertensive population is disturbing as it puts them at a higher risk for premature cardiovascular disease. Early identification and treatment of persons with prediabetes has the potential to reduce or delay the progression to overt diabetes and reduce the associated cardiovascular complications (Glenn et al, 2010).

4.3.1. Lifestyle Interventions

Lifestyle changes are extremely important in preventing progression from prediabetes to overt diabetes mellitus (Knowler et al, 2002). The ADA treatment of choice for patients with prediabetes is lifestyle modification consistent with a 5-10% weight loss and increased physical activity of 30 min/day. The Diabetes Prevention Program study examined more than 3,200 overweight or obese adults with prediabetes and showed that lifestyle interventions, such as those taught in diabetes education programs, reduced the incidence of diabetes by 58% overall and by 71% for older adults (DPPRG, 2002). Lifestyle changes also reduce other risk factors in this population, positively impacting mortality (Tuomilehto et al, 2001). However, lifestyle changes may be difficult to enforce in an older hypertensive population.

4.3.2. Pharmaceuticals

Therapeutic interventions have also been studied in this population to help preserve or restore normal glucose tolerance and insulin sensitivity by improving islet function (DPPRG, 2002). Prediabetic subjects when treated with metformin, show a 31% reduction in the development of diabetes mellitus (Ratner et al, 2005; Orchard et al, 2005). Although TDZs, acarbose and orlistat also reduce incident diabetes, metformin is the preferred choice given its favorable overall safety, tolerability, efficacy and affordability. In patients with associated hypertension, AACE and other profressional associations recommend that blood pressure be maintained at

130 systolic and 80 diastolic or below with ARB or ACE as the first choice of anti-hypertensive agents. Calcium channel blocking agents may be used as second line drugs. Thiazides and beta blockers my worsen glycemia and should only be used third line and with caution. Low dose aspirin may be used provided there are no GI contraindications. Prediabetes is also characterized by an abnormal lipid profile, contributing to an acceleration of atherosclerosis (Magge et al, 2012). Therapeutic modulation of the lipid profile helps benefit these patients with combined hypertension and prediabetes. AACE recommends achieving levels of LDL less than 100 mg/dl, non-HDL cholesterol less than 130 mg/dl and apolipoprotein B below 90 mg/dL. IGT patients may benefit more from fibrate treatment, whereas IFG subjects may be better candidates for statin therapy (Krysiak et al, 2010). Niacin may worsen the glycemic profile and should be avoided.

4.3.3. Benefits of Early Intervention

Early intervention in prediabetics has noticeable clinical benefits - there is a decrease in microvascular complications, such as retinopathy, nephropathy, neuropathy and amputations and a reduction in macrovascular complications such as coronary heart disease, stroke, peripheral vascular disease and congestive heart failure (Zachary et al, Parts I, II and III, 2008). And finally, patients with prediabetes and hypertension should be monitored more frequently. An annual glucose tolerance test and twice-yearly testing for micro-albuminuria and fasting plasma glucose, hemoglobin A1C, and lipid levels are indicated (AACE, 2008).

5. CONCLUSION

We found an extremely high prevalence of prediabetes in our hypertensive population. Prediabetes was present in 46% of these patients. Most hypertensive patients with prediabetes have similar cardiovascular risk factors as patients with type 2 diabetes, such as dyslipidemia, obesity, physical inactivity, insulin resistance, a procoagulant state, endothelial dysfunction and vascular inflammation. This places these prediabetic patients with hypertension at a much high risk for premature cardiovascular morbidity and mortality. These patients should be therefore monitored more frequently and treated aggressively, both with lifestyle modifications and targeted pharmaceuticals.

SUMMARY OF RESEARCH

The frequent co-existence of prediabetes and hypertension is not surprising as they both share several common risk factors, such as obesity and physical inactivity. There may also be a causal association between the two. Since both increase major cardiovascular events, their combined presence demands a much more aggressive management.

FUTURE ISSUES

1.Can new pharmaceutical agents target both dysglycemia and hypertension?
2.Do pre-hypertension and prediabetes co-exist? What are the clinical implications?

DISCLOSURE STATEMENT

The author has no conflicts of interest to disclose.

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