Diabetes and the Younger/Middle-Aged Hypertensive Subject; Obesity, Sympathetic Nerve Activity and Treatment Implications

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Abstract

Introduction

In the last 30 years or so there has been a global increase in obesity [1], being particularly apparent in the USA [1,2] the UK and Australia [3,4]. Obesity tends to be less prevalent among educated wealthy individuals [2].

Weight-gain is associated with an increased risk of type-2 diabetes (DM2) [5]. DM2 is associated with a two-fold increase in cardiovascular events [6]. Weight-gain, in addition to other life-style factors such as physical inactivity, a Westernized diet and alcohol-abuse, is also responsible for about 70% of cases of essential hypertension (HT) in younger/middle-aged subjects [7,8].

This mini-review sets out to examine the inter-relationships between obesity, DM2, and HT, and to highlight the importance of raised sympathetic nerve activity (SNA) and treatment implications.

Essential Hypertension, Obesity, Sympathetic Nerve Activity, Resting Heart Rate, Plasma Renin Activity (Pra), and Prognostic Implications

The classic Framingham Study has investigated the origins of essential HT in a normal (primarily white) population [9] (Table 1). It is apparent that (1) The development of diastolic (± systolic) HT is closely associated to a younger age and an increased body mass index (BMI), and (2) The development of isolated systolic HT occurs in an older age-group, reflecting stiffening/aging of the arteries. Essential HT in the younger age-group is linked primarily to an increased cardiac output [10], while in the elderly (say greater than 60 years old), where there is a fall in cardiac output [11,12], high BP is dependent upon an increased peripheral resistance.

Obese adolescents with HT experience a substantial fall in BP after weight-loss following bariatric surgery, with 74% becoming normotensive [13]. In younger subjects, obesity (particularly central) is linked to a significant increase in SNA in muscle [14] (Figure 1). In men, there is a powerful linear relationship between waist circumference and SNA [15] (Figure 2). Obesity-related increases in SNA are particularly apparent in the presence of HT [16], especially if DM2 is also present [17] (Figure 3). The raised SNA is associated with the release of leptin (so-called “thin hormone”) from central adipose tissue; leptin acts upon the hypothalamic region of the mid-brain, resulting in increased SNA [18]. High insulin levels, associated with obesity-related insulin resistance, also act upon the hypothalamic region, resulting in heightened SNA [19,20].

High levels of SNA are associated with a poor long-term prognosis. Firstly, high norepinephrine (noradrenaline) levels are associated with the atherosclerotic process [21] and (via an increased heart rate) coronary plaque rupture [22]. Secondly, high plasma norepinephrine levels, independent of smoking and blood pressure levels, are powerful predictors of cardiovascular death and survival in young/middle-aged hypertensive subjects over a 6-7 year follow-up period [23] (Figure 4). Importantly, high intra-lymphocyte beta-receptor density (Bmax) and cyclic adenosine monophosphate (DMP) levels predict (independent of BP) future myocardial infarctions, but not stroke (which relates to BP) [23] (Figure 5).
High resting heart rates are a surrogate for increased SNA. The Framingham Study [24] has shown that in young/middle-aged hypertensive subjects, high resting heart rates (particularly over 85 bpm) have been shown to predict all-cause death and cardiovascular and coronary heart disease events for both hypertensive men- (Figure 6) and women, over a 36 year follow-up period.

Beta-1 stimulation of the renal juxtaglomerular apparatus results in the release of renin. Thus, high plasma renin activity (PRA), like high sympathetic activity [23], could be an indicator of a poor prognosis. It is noteworthy that in high PRA cases, beta-blockers have a particularly powerful anti-hypertensive effect [25].

**Therapeutic Implications in Young/Middle-Aged Hypertension with or without DM2**

Antihypertensive agents that increase SNA have performed poorly in terms of reducing cardiovascular events in young/middle-aged hypertensive subjects.

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**Table 1: Different Predictors of Diastolic Hypertension (DH) (± raised systolic–SDH) and Isolated Systolic Hypertension (ISH)–FRAMINGHAM Study [9].**

<table>
<thead>
<tr>
<th>Predictors of Diastolic Hypertension (± Systolic Hypertension)=DBP ≥ 90 mmHg (± SBP ≥ 140 mmHg)</th>
<th>Predictors of Isolated Systolic Hypertension=SBP ≥ 140 mmHg+DBP&lt;90 mmHg (wide P-P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Young age</td>
<td>1. Older age</td>
</tr>
<tr>
<td>2. Male sex</td>
<td>2. Female sex</td>
</tr>
<tr>
<td>3. High BMI at baseline</td>
<td>3. Increased BMI during follow-up (weak)</td>
</tr>
<tr>
<td>4. Increased BMI during follow-up</td>
<td>4. ISH arises more commonly from normal and high normal BP, than “burned out” diastolic hypertension</td>
</tr>
<tr>
<td>5. Main mechanism of DH and SDH is raised peripheral resistance</td>
<td>5. Only 18% with new – onset ISH had a previous DBP ≥ 95 mmHg</td>
</tr>
<tr>
<td>6. Main mechanism of ISH is increased arterial stiffness=aging of arteries</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1:** In 30 lean (L), 20 peripherally obese (PO) and 26 centrally obese (CO) subjects (mean age 36y), muscle sympathetic nerve activity (MSNA) was significantly higher in CO than PO and L subjects. Grassi G et al. 2004 [14]

**Figure 2:** Relationship between waist-circumference and muscle sympathetic nerve activity (MSNA) in men. Joyner MJ et al. 2010 [15]

**Figure 3:** In 68 matched subjects (n=17-NT; 17-DM2; 17 HT; 17 DM2+HT), sympathetic activity markedly raised in DM2+HT, and correlated with high insulin levels. Huggett RJ et al. 2003 [17]

**Figure 4:** 601 middle-aged hypertensive subjects followed-up for 6-7 years; high plasma norepinephrine concentrations (NE) (> 4.0 nmol/L = red) vs low (> 4.0 nmol/L =blue) were associated with high levels of all-cause death (independent of blood pressure). Peng Y-X et al 2006 [23]

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Thiazide-type diuretics increase SNA [26], and in 3 studies involving diuretic therapy in young/middle-aged hypertensive subjects [27-29] there was no reduction in the risk of myocardial infarction, and even a significant increase [29], versus randomised placebo/non-treatment.

Dihydropyrididine calcium blockers increase heart-rate and plasma norepinephrine levels [30], and in the ABCD study involving middle-aged hypertensive subjects with DM2 [31], the investigation was terminated prematurely due to a significant excess of myocardial infarctions in the nisoldipine, vs the enalapril, group.

Angiotensin receptor blockers (ARBs) increase SNA in younger subjects [32,33]. Meta-analyses indicate that, in contrast to ACE-inhibitors, ARBs increase the risk of myocardial infarction [34,35] (Figure 7). In two subsequent placebo-controlled studies involving hypertension [36] and pre-hypertension plus DM2 [37] (Figure 8), there was a significant excess of fatal cardiovascular events in those receiving the ARB.

ACE inhibitors reduce SNA [38], and performed well vs the calcium blocker nisoldipine in terms of fewer myocardial infarctions [31]. In the classic UKPDS-39 study [39], involving middle-aged hypertensive subjects with DM2, atenolol was compared to captopril in terms of reduction of 7 primary endpoints versus less-tight control (10/5 mg Hg) of BP, over a 9 year period of observation. The effects of the 2 agents upon the 7 primary endpoints (plus heart failure, a secondary endpoint), vs less-tight control, are shown in Figure 9. It is apparent that all 8 trends favoured atenolol (over captopril). Compared to less-tight control of BP, atenolol reduced stroke-risk by about 50%, peripheral arterial disease-related endpoints by about 60%, micro-vascular (kidney and eye) endpoints by about 45%, and heart failure by about 65%. After 14.5 years long-term follow-up, the above trends persisted but now there was a significant (23%) reduction in all-cause death in favour of atenolol [40] (Figure 10).

The Important Beta-Blocker/Smoking Interaction in Younger/Middle-Aged Hypertensive Subjects

In 3 major prospective, randomised, hard-endpoint studies in middle-aged hypertensive subjects, cigarette smoking played a key role in modifying the potential of the BB to reduce the risk of a cardiovascular event. The MRC-1 study [28] compared non-selective propranolol with a thiazide diuretic and placebo; the IPPPSH study [49] compared non-selective oxprenolol with placebo; the MAPHY [50] compared moderately beta-1 selective metoprolol with a thiazide diuretic.

How can these events relating to smokers be explained and avoided? Cigarette smoking is linked to a two-to-threefold increase in plasma epinephrine (adrenaline) levels [51]. Epinephrine stimulates beta-1, beta-2 and alpha-receptors, and in the presence of non-selective BBs (and to a lesser extent with only moderately beta-selective agents like metoprolol and atenolol) there is unopposed (total or partial) alpha-vasoconstriction, resulting in an increase in BP [52]. This increase in BP is about 30 mm Hg for non-selective BBs and about 9-10 mm Hg for a moderately selective agent like bisoprolol (which permits full beta-2 stimulation-induced vasodilatation [53,54] (Figure 14).
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Choice of Beta-Blocker

a) Pharmacokinetic properties

These properties have been described [55] (Table 2). As a general rule:

1. Agents with a plasma half-life of 6 hours or more may be dosed on a once daily basis.
2. Liver-metabolised agents, e.g., metoprolol, should be avoided in patients with hepatic dysfunction; in such cases use either a renally excreted agent like atenolol, or an agent with a balanced metabolism/renally excreted profile such as bisoprolol.
3. In patients with renal dysfunction, avoid renally excreted agents like atenolol; in such cases use either a liver-metabolised agent like metoprolol, or bisoprolol (balanced metabolism/excretion).
4. Agents that are metabolised via the hepatic cytochrome P450 system are vulnerable to genetic polymorphism. Thus, nebivolol [56] and metoprolol [57], in poor metabolisers, experience a 3 to 5-fold increase on peak blood levels, leading to loss of beta-1 selectivity and a possible increase in adverse reactions such as fatigue (metoprolol) [58]. Such poor metabolisers account for 8-10% of the UK White population [59], and possibly 30% of Chinese [60].

b) Pharmacodynamic properties

1. Beta-1 selectivity (cardioselectivity): Beta-1/beta-2 selectivity ratios are shown in figure 15 [53]. ICI 118,551 is a pure beta-2 selective antagonist; propranolol inhibits beta-1 and beta-2 receptors equally; metoprolol, atenolol, and betaxolol are only moderately beta-1 selective; bisoprolol is highly beta-1 selective. Beta-1 selectivity is diminished/lost at higher doses (e.g., greater than 10 mg/day of bisoprolol [61]). Nebivolol is not beta-1 selective, as it occupies and stimulates (ISA) the beta-3 receptor (see later).

2. Intrinsic sympathomimetic activity (ISA): The ISA of agents like oxprenolol and pindolol acts via the beta-1 and beta-2 receptors [62], while the ISA of nebivolol acts via the beta-3 receptor [63]. Stimulation of the beta-2 [64] and beta-3 [65-67] receptor (via ISA) results in release of nitric oxide (NO) and vasodilatation. It is worth noting that BBs with ISA are less effective in treating heart failure than BB with no ISA [55]. In the failing heart, beta-3 stimulation worsens cardiac function, and in the post-myocardial infarction period, L-arginine (a substrate for nitric oxide (NO)) significantly increases mortality compared to placebo [68].

3. Alpha-blocking properties: Both labetalol and carvedilol are non-selective for the beta-1 and beta-2 receptors, but contain additional alpha-blocking properties. Such agents lower peripheral resistance [69], and lower heart rate less than traditional beta-blockers [70].

4. Antihypertensive effects in young/middle-aged subjects: Beta-2 blockade results in a rise in BP of about 7/5 mmHg [71]. Thus moderately beta-1 selective atenolol lowers BP more effectively than non-selective propranolol [72]. Atenolol in turn, is a less effective antihypertensive agent than highly beta-1 selective bisoprolol [73]. Indeed, in middle-aged hypertensive subjects bisoprolol is a more effective antihypertensive agent than amlopidine, doxazosine, lisinopril, and bendrofluazide [74] (Figure 16). Bisoprolol is also more effective at reducing BP than angiotensin receptor blockers [75], being at least as renos-protective as the latter [76]. Bisoprolol lowers BP equally in White and Black middle-aged hypertensive subjects [77,78].

5. Adverse reactions: Certain generalised statements are possible [55]:

  a) Lipophilic (lipid soluble) agents, e.g., propranolol and metoprolol (Table 2), readily cross the blood brain barrier, resulting in an increased risk of sleep problems, dreaming and nightmares.

  b) High beta-1 selectivity, e.g., bisoprolol, is compatible with a better “quality of life” compared to non-selective propranolol.

  c) Postural hypotension/dizziness can be troublesome with agents possessing alpha-blocking properties, e.g., labetalol and carvedilol.
<table>
<thead>
<tr>
<th>β-Blocker</th>
<th>Lipid solubility</th>
<th>Extent Absorbed (% dose)</th>
<th>Time to peak blood level (hr)</th>
<th>Plasma half-life (hr)</th>
<th>First-pass (liver) elimination (%)</th>
<th>Systemic bioavailability (%)</th>
<th>Metabolized (hepatic)</th>
<th>Active Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atenolol</td>
<td>x</td>
<td>40-60</td>
<td>2-4</td>
<td>6-10</td>
<td>0</td>
<td>50</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>xx</td>
<td>&gt;90%</td>
<td>2-3</td>
<td>10-12</td>
<td>&lt;10</td>
<td>90</td>
<td>Yes (50%)</td>
<td>No</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>xxx</td>
<td>85</td>
<td>1.5</td>
<td>6-7</td>
<td>60-75</td>
<td>25</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Labetalol</td>
<td>xxx</td>
<td>&gt;90</td>
<td>1-2</td>
<td>3-6</td>
<td>60-70</td>
<td>30-40</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>xxx</td>
<td>&gt;90</td>
<td>1-3</td>
<td>3-4</td>
<td>25-50</td>
<td>50-75</td>
<td>Yes</td>
<td>Yes (Weak)</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>xxx</td>
<td>90</td>
<td>1-4</td>
<td>13</td>
<td>70</td>
<td>12-96</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxprenolol</td>
<td>xx</td>
<td>90</td>
<td>1-1.5</td>
<td>1-2</td>
<td>25-80</td>
<td>20-75</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Pindolol</td>
<td>xx</td>
<td>&gt;90</td>
<td>0.5-1</td>
<td>2-5</td>
<td>20</td>
<td>80</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Propranolol</td>
<td>xxx</td>
<td>&gt;90</td>
<td>1-3</td>
<td>3-4</td>
<td>70</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Sotalol</td>
<td>x</td>
<td>&gt;90</td>
<td>2-3</td>
<td>7-15</td>
<td>0</td>
<td>&gt;90</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Timolol</td>
<td>xxx</td>
<td>&gt;90</td>
<td>1-4</td>
<td>2-5</td>
<td>50-60</td>
<td>40-50</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 2: Pharmacokinetics of commonly used beta-blockers


d) Fatigue/lethargy can be a problem with BBs, particularly at higher doses, or in slow metabolisers of metoprolol [58]. For patients involved in aerobic pursuits, non-selective agents should be avoided (blockade of muscle beta-2 receptors), with preference given to highly beta-1 selective agents like bisoprolol [79,80].

e) Cold peripheries can be troublesome, but are less likely with highly beta-1 selective agents or, when ISA or alpha-blocking properties are also present.

f) Renal function can be reduced by non-selective BBs, while moderately beta-1 selective atenolol was at least reno-protective as captopril in the UKPDS-39 study [39], and bisoprolol was at least as renoprotective as the ARB losartan [76].

g) In reversible airways disease, high beta-1 selectivity is advantageous i.e. increasing airways resistance (brochospasm) is less likely, and beta-2 induced broncho-dilatation is permitted.

h) Metabolic disturbance is less likely with highly beta-1 selective agents such as bisoprolol i.e. less risk of disturbances involving blood lipids and sugar.

i) Weight-gain is less likely with highly beta-1 selective agents.

j) Sexual dysfunction (vs randomised placebo) is most common among agents that display combined beta-1, beta-2, and alpha blocking properties e.g. carvedilol, followed by non-selective propranolol and moderately selective atenolol, and can be avoided by high beta-1 selectivity e.g. bisoprolol.

References


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