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ORIGINAL ARTICLE

Clinical characteristics of two groups commonly referred to an Irish hypertension service—patients with resistant hypertension and young adults with hypertension

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Abstract

Background The management of hypertension is primarily performed in primary care settings in many health systems. However, two groups of patients often require specialist input: patients with resistant hypertension (RH) and young adults with hypertension.

Aims To elucidate these groups by examining the characteristics of patients attending an Irish hypertension service, thus informing future management of hypertension.

Methods Patients were recruited at consecutive hypertension clinics at St James Hospital, Dublin from July to September 2019. Following patient consent, patient data were recorded to identify patient characteristics as well as the results of investigations, blood pressure (BP) measurements and the anti-hypertensive treatment of the study participants which were then analysed.

Results Two hundred thirty-six patients were included in the study. Compared to those without RH, the RH group were more likely to be obese (OR 2.59 [95% CI 1.06 to 6.33]), to have cardiovascular disease (OR 3.07 [95% CI 1.56 to 6.02]) and to have a non-dipping BP pattern (OR 3.86 [95% CI 1.57 to 9.47]).

Young adults comprised 27% of the cohort. Forty-seven percent of these patients were obese, 15.9% had hypertension in pregnancy and 22.2% had chronic headaches. Despite being prescribed less anti-hypertensives (1.41 vs 2.28; $p < 0.05$), the majority of young patients had a BP less than 140/90 mmHg, comparing favourably with older patients (OR 2.25 [95% CI 1.20 to 4.27]).

Conclusion This contemporary study highlights the high prevalence of obesity among RH patients and young adults with hypertension. Findings suggest that programs to combat hypertension must include interventions to address obesity.

Keywords Hypertension clinic · Obesity · Resistant hypertension · Young adults

Background

Most of the care for hypertension is provided in a primary care setting. There is a paucity of recent studies characterising patients attending specialist hypertension clinics, with much research around hypertension focusing on systematic reviews, meta-analyses of previous studies and public health aspects of the condition. From our practice, and in line with international guidance, two groups of patients are frequently referred to our specialist hypertension clinic — those with resistant hypertension (RH) and young adults with hypertension. A contemporary characterisation of these cohorts may inform their clinical management.

Resistant hypertension is variably defined but most guidelines agree that the term refers to patients whose blood pressure remains uncontrolled blood pressure while on three anti-hypertensive agents, including a diuretic [1, 2]. Patients with RH should be considered for a referral to a specialist hypertension clinic to achieve blood pressure (BP) control [1]. Estimates for the prevalence of RH

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show significant variation from 2.9 to 43% depending on the population studied and RH definition used [3–7]. RH patients are more likely to be older, male and black [8]. RH is associated with obesity, obstructive sleep apnoea (OSA), left ventricular hypertrophy (LVH), chronic kidney disease (CKD), type 2 diabetes mellitus (T2DM) and metabolic syndrome [6–9].

A second group frequently referred to a specialist hypertension clinic are young adults with hypertension; those between the ages of eighteen and thirty-nine [1, 10]. It is difficult to determine the prevalence of hypertension in young adults, though observational data from a US cohort provided a figure of 19% for those aged twenty-four to thirty-two, though just 4% of adolescents in NHANES had hypertension [11, 12]. Compared to older adults, young adults with hypertension have poorer awareness of the condition, are less likely to be treated and much less likely to have their blood pressure controlled as a result [11, 13]. Much of the evidence regarding young adults with hypertension is derived from the US-based CARDIA study [14]. However, this cohort was recruited in 1985–1986 and thus does not provide an up-to-date profile of young adults with hypertension.

The aims of this study included:

i. Determining the clinical characteristics of patients with RH attending a specialist hypertension clinic to compare to those without resistant hypertension and previously described cohorts, as well as identifying their anti-hypertensive regimens.
ii. Describing the cohort of young patients attending the clinic in terms of comorbidities to identify subgroups, based on their comorbidities and risk factors, who may warrant further elucidation and management protocols.

Methods

Study setting and consent

The methods of this study have been described previously [15]. This study was initiated in July 2019 and involved patient recruitment over a 3-month period at the Hypertension Clinic at St James's Hospital, Dublin. The study was observational and pragmatic so the workflow of the clinic was not disrupted.

Consent for inclusion in the study was requested from all adult (18 years and older) patients attending the specialist hypertension clinic at St James's Hospital whose primary issue was hypertension. The study was GDPR compliant and approved by our institutional Research Ethics Committee.

Data collection and analysis

Clinical and sociodemographic data were extracted from the patient's medical record at their current visit. A diagnosis of cardiovascular disease (CVD) was taken as a disease affecting cardiac or vasculature system, e.g. ischemic heart disease (IHD), coronary artery disease (CAD), peripheral vascular disease, stroke, transient ischemic attack (TIA), cardiac arrhythmia, valvular heart disease and congestive cardiac failure (CCF) [16]. A mental health illness was one of the following: depression, generalised anxiety, bipolar affective disorder and schizophrenia. Patient height was measured at the first clinic visit and weight was routinely taken at every clinic visit (unless the patient refused or could not be weighed), allowing body mass index (BMI) to be calculated. The patient's medications were derived from their medical record. The patient's updated medication list and their adherence to the medication is checked during each consultation (the study did not include further measures of medication adherence).

Methods for clinic and ambulatory BP were previously described at length [15]. Clinic blood pressure was compared to recommended targets in the recent European Society of Hypertension (BP < 130/80 mmHg for those under 65 years and < 140/80 mmHg for those ≥ 65) and American Hypertension Association guidelines (BP < 130/80 mmHg) as well as a target of < 140/90 mmHg recommended by the National Institute of Health and Care Excellence [1, 2, 17]. Non-dipping blood pressure was as described in the 2018 ESC/ESH guidelines, a ratio of > 0.9 when average night BP is compared to daytime average on ABPM. A diagnosis of moderate/severe CKD was made if the patient's estimated glomerular filtration rate (calculated using the Modification of Diet in Renal Disease formula) was < 60 mL/min per 1.73 m^2 on two occasions 3 months apart [18]. The term 'hypertension in pregnancy' was used if a diagnosis of hypertension was made during a previous pregnancy in a manner consistent with the ESC/ESH definition [1].

Those with RH were identified as being on three anti-hypertensive drugs, including at least one diuretic, and not having office systolic and diastolic BPs less than 140 mmHg and/or 90 mmHg, respectively, or those on four or more anti-hypertensive drugs [1]. If a valid ABPM was available, white coat hypertension (WCH) was also excluded before the patient was included in the RH group. Young adults with hypertension were those between the ages of 18 and 39 years of age at the first visit to the clinic. Hypertension mediated organ damage (HMOD) was identified by available tests results including LVH on echocardiogram reports, CKD and/or proteinuria/albuminuria confirmed by protein/albumin creatinine ratio. Statistical analysis included standard two tailed *t*-test for continuous variables and the chi-squared

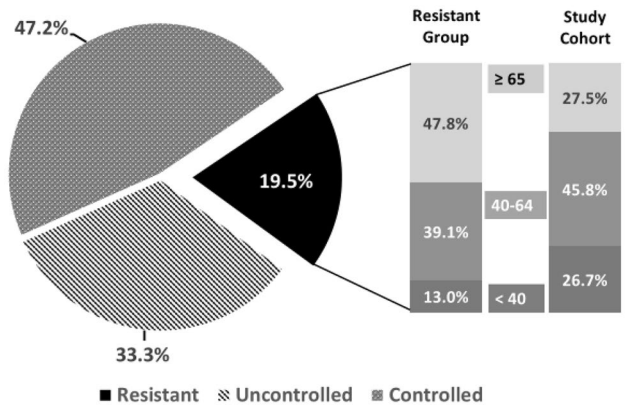

Fig. 1 Study blood pressure groups including the age breakdown of the patients with resistant hypertension and the full study cohort for comparison. Legend: A clinic blood pressure less than 140/90 mmHg was considered controlled

test for differences in proportions. Chi-squared tests included risk analyses with odds ratio and confidence intervals as outputs. As standard, the minimum level of statistical significance was 5% ($p < 0.05$). Analyses were performed using Microsoft Excel and SPSS software version 25 (IBM Corp, Armonk, NY, USA).

Results

Resistant hypertension

Clinical characteristics

A total of 236 participants were enrolled in this study between July and September 2019. Anthropological measurements were available for 171 patients and 120 had a valid ABPM. Patients with RH constituted 19.5% of the study cohort, while the majority of the study cohort without RH had a blood pressure in the controlled range (Fig. 1). Of note, 87% of the RH had a valid ABPM which enabled the exclusion of WCH in these cases. Figure 1 shows that those with RH were older (61.7 versus 50.7 years, $p < 0.001$) and more likely to be ≥ 65 years (odds ratio [OR] 3.13, 95% confidence interval [CI] 1.60 to 6.13, $p = 0.001$).

Table 1 shows the clinical characteristics of RH patients compared to non-resistant. A female predominance was evident for the study cohort, and this was reflected in the resistant group. Average BMI for RH patients was 34 kg/m^2 and RH patients were significantly more likely to be obese (OR 2.57, 95% CI 1.06 to 6.24, $p = 0.033$). Indeed, 69.2% of RH patients were obese and 96% were either obese or overweight. Other components of metabolic syndrome were evidently increased in the RH group; more RH patients had hypercholesterolemia (OR 2.61, 95% CI 1.35 to 5.05, $p = 0.004$) and type 2 diabetes mellitus (OR 2.65, 95% CI 1.13 to 6.23, $p = 0.021$).

Both resistant and non-resistant groups had similar percentage of patients diagnosed with mental health illness, 17.4% in each group. In terms of lifestyle factors, a quarter of the RH group were currently, or had previously, consumed alcohol to excess compared to 13.6% of the non-RH group (OR 2.23, 95% CI 1.02 to 4.84, $p = 0.040$) though there was no significant difference in smoking rates (Table 1).

A non-dipping nocturnal BP pattern was highly prevalent in the RH group at 79.4%, while this pattern was identified in 50% of the non-RH patients (Fig. 2, OR 3.86, 95% CI 1.57 to 9.47, $p = 0.002$). Consistent with this finding, and with the prevalence of obesity in the RH group, OSA was a more frequent comorbidity in RH patients (OR 4.08, 95% CI 1.40 to 11.93, $p = 0.006$).

In terms of the consequences of hypertension, those with RH were more likely to have HMOD (OR 4.44, 95% CI 2.17 to 9.10, $p < 0.001$) and a prior diagnosis of CVD was more often reported in the RH group (50%) compared to the non-RH group (26%). One-third of RH patients had chronic kidney disease, again a higher prevalence compared to the non-RH group (OR 4.10, 95% CI 1.88 to 8.97, $p < 0.001$).

Anti-hypertensive medications

The majority of the RH patients were taking calcium channel blockers (83%) and either an angiotensin converting enzyme inhibitor (ACEi) or an angiotensin-II receptor blocker (ARB) (96%). Also, 63% of RH patients were on a thiazide or thiazide-like diuretic. Figure 3 illustrates the different anti-hypertensive agents which may be considered for fourth-line use, comparing the RH and non-RH groups. A considerable number of RH patients were on beta-adrenergic blockers (57%) while a small percentage were prescribed nitrates. These may reflect the high prevalence of CVD in the RH cohort. Alpha-adrenergic blockers were used with considerable frequency, though prescribed infrequently in the non-RH group ($p < 0.001$). Mineralocorticoid receptor antagonists (MRAs) were rarely prescribed in the non-RH group (0.5%), though their use was more apparent in the RH group (17%).

Young patients with hypertension

Young adults comprised 26.7% of the study cohort. Many of the clinical characteristics reported by the study did not differ significantly between the young adults and older adults

Table 1 Patient characteristics of those with resistant hypertension compared to non-resistant hypertension ($n=236$)

Characteristic	Resistant (%) ($n=46$)	Non-resistant (%) ($n=190$)	Odds ratio	95% Confidence interval	p value
Male	41.3	45.2	0.85	0.44 to 1.64	0.628
Elderly (≥65 years)	47.8	22.6	3.13	1.60 to 6.13	0.001
Young (<40 years)	13.0	30.0	0.35	0.14 to 0.87	0.020
Overweight	26.9	34.0	0.71	0.28 to 1.82	0.478
Obesity	69.2	47.0	2.59	1.05 to 6.33	0.033
Hypercholesterolemia	60.8	37.3	2.61	1.35 to 5.05	0.004
Type 2 diabetes	21.7	9.5	2.65	1.13 to 6.23	0.021
Cardiovascular disease	50.0	26.3	3.07	1.56 to 6.02	0.001
Chronic kidney disease	33.3	10.9	4.11	1.88 to 8.97	<0.001
Mental health illness	17.4	17.4	1.00	0.43 to 2.34	0.997
Alcohol excess	26.0	13.7	2.23	1.02 to 4.84	0.04
Smoker	19.6	14.2	1.47	0.64 to 3.38	0.365
Family history of hypertension	71.7	70.5	1.06	0.52 to 2.17	0.871
Family history of CVD	47.8	50.0	0.92	0.48 to 1.75	0.791
Hypertension Mediated Organ Damage	41.3	13.7	4.44	2.17 to 9.10	<0.001

(those ≥40 years). Among these findings, it is interesting to note that the BMI for the young adults was similar to that of the older adults (30.3 vs 31.5 kg/m^2, $p=0.28$). As expected, the young group had a lower prevalence of CVD (OR 0.20, 95% CI 0.09 to 0.47; $p<0.001$), RH (OR 0.35, 95% CI 0.14 to 0.87, $p=0.020$) and HMOD (OR 0.21, 95% CI 0.08 to 0.64, $p=0.003$).

Subgroups of young adults with hypertension

The most significant finding was prevalence of overweight and obesity among this group of patients (76% combined), the extent of which was unexpected (Fig. 4). Following these findings, the percentages of other conditions were relatively modest. Chronic headaches were frequent and 8% of this group had a diagnosis of migraine. Hypertension in pregnancy was an identifiable subgroup, with possible uncertainty regarding the ongoing management of these patients (e.g. safety of anti-hypertensives in breastfeeding and in future pregnancies), leading to referrals from primary care [15]. For a young cohort, the prevalence of T2DM was high, but correlates with the levels of obesity and metabolic

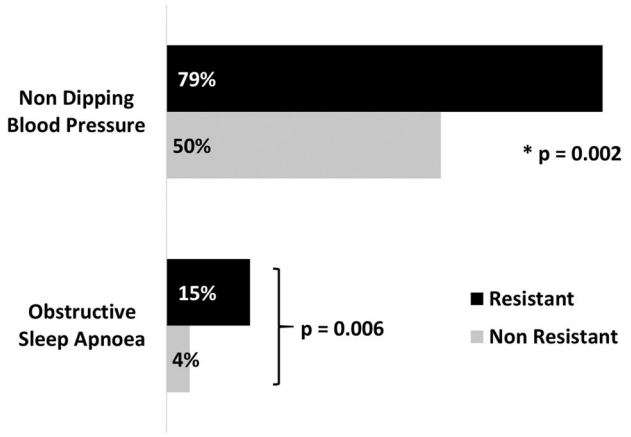

Fig. 2 Comparison of the resistant hypertension patients and those without resistant hypertension in terms of nocturnal blood pressure and obstructive sleep apnoea

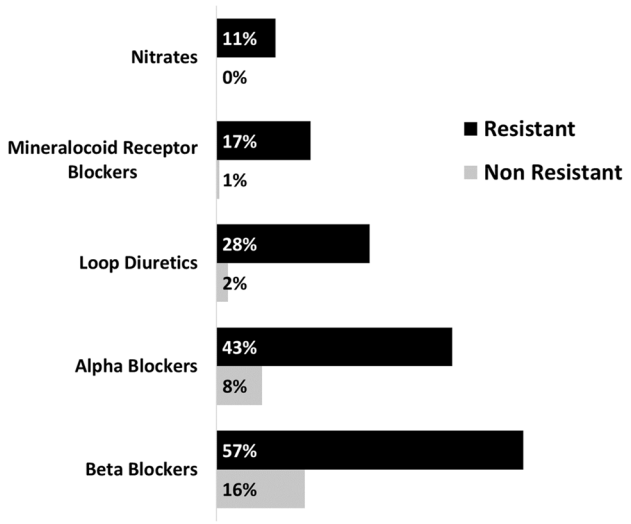

Fig. 3 The anti-hypertensive medications used by patients with and without resistant hypertension. Legend: The anti-hypertensive medications exclude the three most frequently prescribed classes: calcium channel blockers, renin-angiotensin system inhibitors, thiazide diuretics/thiazide-like diuretics

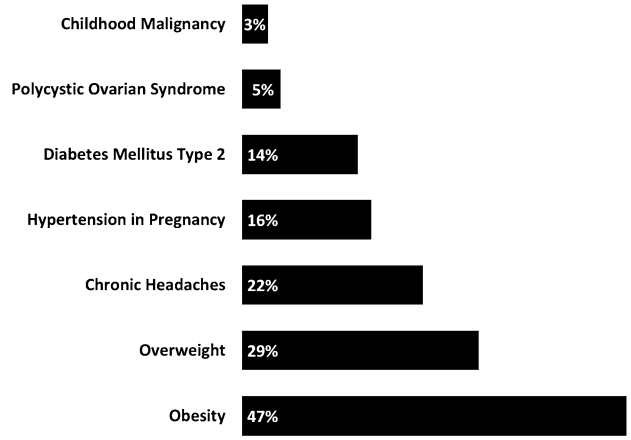

Fig. 4 Comorbidities frequently identified in young adults with hypertension

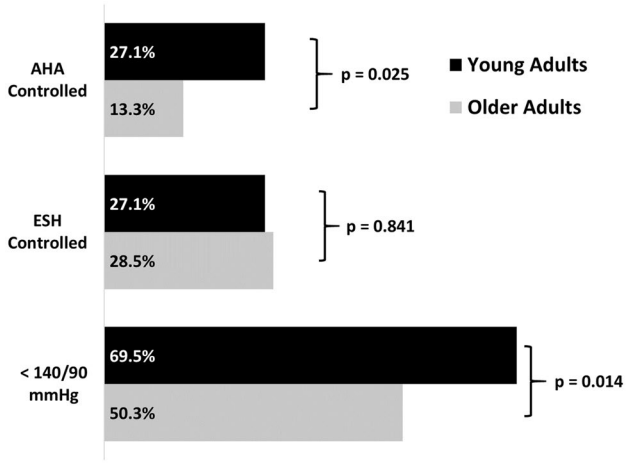

Fig. 5 Percentage of young adults with controlled blood pressure after application of guideline criteria. Legend: ESH, European Society of Hypertension; AHA, American Heart Association

syndrome in this group. While we had expected to detect subgroups such as survivors of childhood malignancies, these cases were rare.

Blood pressure control

The blood pressure control of young adults was favourable compared to the older cohort when a cut-off of 140/90 mmHg was applied as evident in Fig. 5 (OR 2.25, 95% CI 1.20 to 4.24, $p=0.014$). This result was replicated when the AHA cut-off of 130/80 mmHg was used, with better BP control for younger patients (OR 2.42, 95% CI 1.17 to 5.01, $p=0.015$). Interestingly, a different result was reached when ESC/ESH targets for BP control which applies a lower cut-off for patients under 65 years (OR 0.93, 95% CI 0.48 to 1.82, $p=0.841$). Analyses of average, day and night-time BP targets using the ABPM data did not find significant between group differences, though there were less non-dippers in the young group (OR 0.28, 95% CI 0.14 to 0.58, $p<0.001$).

Discussion

Resistant hypertension

In this pragmatic observational study, the RH group, after comparison to those without resistant hypertension, displayed a familiar metabolic syndrome phenotype with increased prevalence of T2DM, hypercholesterolemia and obesity. Indeed, the majority of those with RH had excessive body weight. Also, a non-dipping BP pattern and OSA was more prevalent in the RH group. RH patients were more often found to have HMOD and CVD, reinforcing their categorisation as a cohort with high risk of cardiovascular events. Beta-blockers were used in the majority of RH cases and the use of MRA's was infrequent.

A previous study of patients attending a specialist hypertension clinic in Greece reported a RH prevalence of 12.3%, while 65.5% of patients had uncontrolled hypertension [7]. In general, previous studies have described a 12–14% prevalence of RH of among treated hypertensive patients [19]. Our finding of 19.5% of patients with RH should be considered in the context of our definition of RH for this study which was tailored to the pragmatic design and is closest to that put forward by Carey et al. [8]. The higher RH prevalence here may be due to numerous factors including the relatively small cohort and the inability to assess adherence due to the pragmatic design of the study. Some studies have included the exclusion of WCH in their criteria for RH [20]. While we did include this requirement, 87% of the RH cohort had a recent valid (within the last year and > 70% successful readings) ABPM without WCH.

The previously discussed Greek hypertension clinic cohort also had a high prevalence of excess body weight, with 64.8% being obese compared to the 69.2% reported here [7]. Other relevant comparisons include the number of RH patients with CKD in our cohort (33%) versus the Greek clinic (23.3%), those with T2DM (21.7% vs 15.9%). A report from the Spanish ABPM Registry cohort found half the patients with RH were obese while almost a third had T2DM [20]. A Malaysian cohort in a primary care setting reported even higher levels of T2DM (62.6%) and CKD (53.3%) and a lower average BMI (27.4 kg/m^2), likely due to the South East Asian context and the much older age profile (mean 66.9 years) [6]. To summarise findings across studies, and also evident from this study, those with metabolic abnormalities and a metabolic syndrome phenotype are more

likely to have RH [8]. A central factor driving these derangements, very evident from our study, is excess body weight.

The high prevalence of obesity in our cohort requires reflection. This finding is even more evident in the RH cohort. The underlying pathophysiological processes of obesity include insulin resistance, sympathetic overactivity, salt retention and sleep-disordered breathing [21, 22]. All these processes lead to an increased risk, and prevalence, of CVD and CKD. One of the key intermediates between these pathophysiological pathways and the clinical outcomes is hypertension [22]. Recently, the STEP trials have provided evidence of the benefit of GLP-1 agonists in obese patients in terms of weight loss and a BP lowering effect [23]. SGLT-2 inhibitors may also exert an anti-hypertensive effect in specific populations [24]. Clinical trials of these agents for obese RH patients are a logical next step.

OSA is an important element of this obesity-hypertension milieu [25]. An extremely high prevalence of OSA in patients with RH has been reported in US cohorts (64 to 77%) [26, 27]. Our prevalence is lower and suggests a greater focus is required to identify these patients, particularly if they have RH and obesity, while delays in assessment and diagnosis of OSA in the Irish setting may also factor. The high level of non-dipping nocturnal blood pressure seen in this study is consistent with findings in previous RH cohorts [20, 28]. This leads to several considerations. Firstly, it highlights the importance of completing ABPM at least once for the majority of patients. Secondly, it leads to questions about the dosing period of some anti-hypertensives and chronotherapy. While some anti-hypertensive drugs have a mid to long half-life and demonstrate an effect over a 24-h period, others do not possess such properties [29, 30]. Comorbidities in the RH cohort may affect the half-life due to altered pharmacokinetics, for example percentage body fat and CKD. Given recent evidence suggesting nocturnal dosing of anti-hypertensive drugs improves BP control and may improve CVD outcomes, switching to night-time dosing for the RH cohort should be considered [31, 32]. Further evidence on nocturnal dosing will be available soon when the TIME study reports its findings [33].

RH may be due to increased intravascular fluid retention, increased sympathetic nervous system activity or a combination of both and so the most appropriate anti-hypertensive to add to a standard three-class regimen is the subject of debate [8, 34, 35]. Following PATHWAY-2, the use of MRAs as a fourth-line agent is favoured by ESC/ESH guidance [36]. However, MRAs were not frequently used in our cohort. This may be due to high normal potassium levels, avoiding use in frailer patients, avoidance in those susceptible to hyperkalemia (e.g. advanced CKD), the proximity of this study to the release of ESC/ESH guidance and the possible greater benefit of beta-blockers in those with CVD. This finding requires further investigation.

Young patients with hypertension

While the elucidation of young adults with hypertension identified a small number of patients with previous bone marrow transplant for childhood malignancy and some with PCOS, the main and unexpected finding was that the cohort of young patients was of a similar body weight profile to the older patients. The high prevalence of chronic headaches in this cohort is also of interest and requires more consideration. Those with hypertension in pregnancy compose a significant subgroup as we expected. Another group of note was those with T2DM, reflecting the metabolic derangements associated with obesity. The young patients had significantly less HMOD and CVD than their older counterparts, highlighting the importance of intervening early in these patients. The BP control was better in the young adults though this difference was attenuated by using two age-based cut-offs for BP control as recommended by ESC/ESH guidelines.

The prevalence of obesity in the young subgroup needs to be considered. As well as the obesity-hypertension association, lifestyle factors driving the obesity epidemic predispose young adults to hypertension [37]. It should be expected that greater numbers of young obese patients will be referred to hypertension clinics. Holistic treatment of these patients is required by targeting lifestyle improvements via local and national public health interventions, e.g. community weight loss programs [38]. Pharmacological treatment of obesity may also have a role in terms of BP lowering and CVD prevention.

The subgroup of those with hypertension in pregnancy is notable. Hypertension is a feature of at least 10% of pregnancies [39]. NICE guidance does not describe in detail the management of these patients after the initial postpartum period while European guidance recommends annual checks in a primary care setting [1, 40]. Irish guidance recommends a standard assessment of hypertension which persists after the initial postpartum period of 6 weeks [41]. Given that most of these patients are less than 40 years, this may be interpreted as a recommendation to refer for investigation of a secondary cause. Referrals in this subgroup are often due to either uncertainty regarding the long-term management plan or questions related to the most appropriate anti-hypertensive drugs if the patient is considering conceiving again. Therefore, clearer guidance of the role of a specialist, non-maternity clinic is required.

Interestingly, chronic headache was a frequent feature in young patients attending the clinic (22%, Fig. 4) and reflects headaches in the setting of hypertension as a frequent referral trigger in practice. Headaches are a well described and common presenting symptom of hypertension. However, it may be difficult to discern whether the hypertension causes the headache, the relationship is vice versa or they simply coincide [42]. Observational studies suggest those with migraine may be at increased risk of hypertension in future

and also increased CV risk [43, 44]. However, the association between hypertension and non-migrainous headache may be an inverse one [45]. The use of analgesics which may alleviate headache but increase blood pressure, namely non-steroidal anti-inflammatories, must also be considered. Headaches have multiple aetiologies, triggers and risk factors. A number of considerations will guide the diagnosis and treatment of hypertension in these patients including repeated blood pressure when headache free and out ruling other causes. An improvement in headache symptoms when BP is treated may be an indicator, though a number of anti-hypertensives are used for migraine prophylaxis (beta-blockers, ACEi, ARBs), and so the beneficial effect may be via mechanisms other than BP lowering.

Population-based studies suggest BP control is often poorer in younger patients; however, as seen in Fig. 5, this was not evident in the setting of our clinic [46]. BP control based on ESC/ESH guideline criteria in our cohort was better, though in a similar range, to that seen in a study of three centres of excellence in hypertension [47]. A significant factor accounting for this difference is the younger patient profile attending our clinic, with nearly three-quarters of patients under 65 (Fig. 1) compared to half in the three centre cohort.

Strengths and limitations

Strengths of this study include its pragmatic design which creates a contemporary profile of patients referred to hypertension clinic. The most pertinent limitations are due to the pragmatic and observational study design. Firstly, there is an inability to identify true resistant hypertension as adherence is not formally assessed and intolerances were not recorded. However, despite potentially including those without true resistance in the RH group, the evident patterns are consistent with previous studies. Also, not all patients had every test described, e.g. ABPM. Finally, the long lead time to some investigations may mean the certain diagnoses are understated in this group, e.g. OSA.

Conclusion

This observational study provides insight into a contemporary patient cohort attending an Irish hypertension clinic. Most patients with RH had a non-dipping BP pattern and MRAs were prescribed less frequently than expected. The young adult group often had a background of chronic headaches, hypertension in pregnancy and T2DM. This group had better BP control than their older hypertensive counterparts while requiring less anti-hypertensive drugs to do so. Most significantly, our findings suggest that programs to treat hypertension must include interventions to prevent and treat obesity.

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Author contribution Cormac Kennedy, Richard Farnan and John Stinson contributed to the study conception and design. Material preparation and data collection were performed by all authors. Analysis was performed by Cormac Kennedy, Osama Ali and Richard Farnan. The first draft of the manuscript was written by Cormac Kennedy, Osama Ali and Ahmed Gabr. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Availability of data The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Ethical approval Ethical approval was granted by the Tallaght Hospital Research Ethics Committee.

Consent to participate Informed consent was sought and provided by all study participants.

Consent for publication Informed consent was sought and provided by all study participants.

Competing interests The authors declare no competing interests.

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