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Screening for primary aldosteronism using the newly developed IDS-iSYS® automated assay system

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ABSTRACT

Background: The recommended approach to screening for primary aldosteronism (PA) in at-risk populations is to determine the ratio of aldosterone concentration (serum (SAC)/plasma (PAC)) to renin measured in plasma as activity (PRA) or concentration (DRC). However, lack of assay standardisation mandates the need for method-specific decision thresholds and clinical validation in the local population.

Aim: The study objective was to establish method-specific aldosterone: renin ratio (ARR) cut-offs for PA in men and women using the IDS-iSYS® assay system (IDS plc).

Methods: A prospective cohort study design was used. PAC and DRC were measured immunochemically in ethylenediamine-tetraacetic acid (EDTA) plasma on the IDS-iSYS® instrument.

Results: A total of 437 subjects (218 men, 219 women) were recruited including: healthy normotensive volunteers (n=266) and women taking the oral contraceptive pill (OCP; n=15); patients with essential hypertension (EH; n=128); confirmed PA (n=16); adrenal cortical carcinoma (ACC; n=3); Addison's disease (AD; n=4) and phaeochromocytoma/paraganglioma (PPGL; n=5). In this population, an ARR cut-off at >37.4 pmol/mIU provided 100% diagnostic sensitivity, 96% specificity and positive likelihood ratio for PA of 23:1. When the ARR decision threshold was stratified according to gender, a cut-off of >26.1 pmol/mIU in men and >113.6 pmol/mIU in women resulted in diagnostic sensitivity and specificity of 100%.

Conclusion: This study demonstrates that decision thresholds for PA should not only be method-specific but also gender-specific. However, given the small number of PA patients (n=16), particularly women (n=4), further validation through a prospective study with a larger PA cohort is required before the thresholds presented here could be recommended for routine clinical use.

1. Introduction

Primary aldosteronism (PA), first described by Jerome Conn [1], is a group of adrenal disorders in which aldosterone production

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is inappropriately high for sodium status, relatively independent of angiotensin II stimulation and nonsuppressible by sodium loading [2]. Prevalence rates in hypertensive populations vary from 3% to 32% [3–6]. Patients with PA have higher cardiovascular morbidity and mortality than age-, gender- and blood pressure- (BP) matched subjects with essential hypertension [7,8]. Timely identification is likely to lead to better outcome as specific management has been shown in observational studies to improve the impact of this condition on key patient outcomes [7,9,10]. The recommended approach to screening for PA in at-risk populations is to determine the aldosterone-to-renin ratio (ARR)[2,11]. The ARR is calculated from the concentration of aldosterone in serum (serum aldosterone concentration, SAC) or plasma (plasma aldosterone concentration, PAC) divided by plasma renin measured either as renin activity (PRA) or direct renin concentration (DRC)[11]. However, measurement of aldosterone and renin is analytically challenging, with several method combinations for both analytes in routine clinical use. This situation is further compounded by the lack of assay standardisation and the use of different reporting units for both aldosterone (ng/dL, ng/L, pg/mL and pmol/L) and renin (PRA: ng/mL/h, nmol/L/h and pmol/L/min; DRC: μIU/mL, mIU/L and ng/L). This underlies the need for method-specific decision thresholds and clinical validation in the local population.

The recent Endocrine Society Clinical Practice Guideline (ESCPG) for the management of PA provides assay-dependent ARR decision threshold values reflecting the use of renin activity and concentration, and expressed using different reporting units [2]. Notably, this table is unchanged from that previously published in 2008 [11]. From a clinical perspective this is challenging, as significant methodological improvements have occurred in the intervening eight years. There is no reference to clinical validation studies using these newer assays [12,13]. Moreover, it is often not appreciated that indiscriminate adoption of the ESCPG cut-offs has the potential to incorrectly classify patients [14].

Using the newly developed *Immunodiagnostics Systems Speciality Immunoassay Automated System* (IDS-iSYS® system; IDS plc, Boldon, UK) for aldosterone and renin measurement, we demonstrated that reference intervals for aldosterone, renin and the ARR are gender-specific [15]. The finding of significant differences between genders is an important consideration in relation to how these reference intervals are applied in the stratification of patients with refractory hypertension and optimisation of therapeutic management of patients with hypertension. The objective of this study was to establish method-specific ARR cut-offs for PA in men and women using the IDS-iSYS® assay system.

2. Methods

Research ethics approval for this collaborative study was obtained in accordance with the Declaration of Helsinki and was granted by each Institution's Clinical Research Ethics Committees prior to commencing patient recruitment.

2.1. Study design

2.1.1. Patient cohorts

A prospective cohort study design was conducted at the Centre for Endocrinology, Diabetes and Metabolism at Galway University Hospital (GUH) between December 2014 and September 2015. Redundant ethylene diamine-tetracetic acid (EDTA) plasma from patients presenting to GUH with hypertension (HTN; n=128) or an adrenal mass/pathology (n=28) and with an ARR requested was utilised. Study subjects were investigated according to routine standard medical/diagnostic care [2,16–18]. Clinical details were recorded on a standardised data collection form following chart review and interrogation of the electronic radiology and laboratory information systems.

The inclusion criteria were: age ≥18years, non-pregnant and either exclusion or confirmation of PA by standard criteria that were necessarily independent of the biochemical tests being evaluated (specifically, the aldosterone response to the Saline Infusion Test (SIT) or an established alternative diagnosis).

Those with specific diagnoses were included based on the following criteria:

PA: diagnosis confirmed by pathological SIT i.e., PAC >140 pmol/L post the infusion of 2 L of normal saline (0.9% NaCl) over 4 h [12]: Phaeochromocytoma/Paraganglioma (PPGL)/Adrenal Cortical Carcinoma (ACC): diagnosis confirmed histologically; Addison's disease (AD): confirmed by response to short synacthen test i.e., 30 min post synacthen cortisol <430 nmol/L (Method: Cobas® Cortisol assay [Roche Diagnostics, Basel, Switzerland); Treated essential hypertension (EH): Type 2 Diabetes Mellitus (T2DM) with haemoglobin A_{1C} ≤75 mmol/mol on a minimum of 2 anti-HTN agents excluding β-blockers; Treatment-naïve EH: non-diabetic with normal electrolytes and kidney function (Modification of Diet in Renal Disease Study [MDRD] equation eGFR >60 mL/min/1.73 m^2). Not all patients in the treated EH or treatment-naïve EH groups had a SIT to definitively exclude PA. The decision not to perform the SIT was based on the initial clinical presentation, the degree of hypertension and the number of antihypertensive medications required to control the hypertension.

The exclusion criteria were: insufficient sample volume (<500 μL) or gross haemolysis/ lipaemia.

2.1.2. Healthy volunteers

Data for ARR from 266 participants recruited from the local population with the objective of establishing reference intervals for PAC, DRC and the ARR and previously published were utilised in this study [15]. In brief, the inclusion criteria for healthy volunteers were; age ≥18years, BMI ≤30 kg/m^2, non-pregnant, BP <140/90 mm Hg, normal electrolytes and kidney function (MDRD equation eGFR≥60 mL/min/1.73 m^2), non-smoker, Irish Caucasian, and not taking prescribed/Over The Counter (OTC) medications for a minimum of 3 months. In female participants of reproductive age, no record of the stage of the menstrual cycle was taken at the time of sample collection.