The spectrum of low-renin hypertension

(Article begins on next page)

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1   THE SPECTRUM OF LOW-RENIN HYPERTENSION

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12   **Abstract**

13   Low-renin hypertension (LRH) is a frequent condition in patients with arterial hypertension,

14   accounting for 30% of patients. Monogenic forms can cause LRH in a minority of cases.

15   However, in the large majority of patients, LRH is caused by the combined effects of

16   congenital and acquired factors, comprising dietary habits. Several genetic variants have been

17   proposed as co-factors in the pathogenesis of LRH with normal-low serum aldosterone.

18   Emerging evidences support the hypothesis that a large proportion of LRH with normal-high

19   serum aldosterone is associated with subclinical primary aldosteronism (PA). The recent

20   identification of aldosterone-producing cell clusters (APCCs) as the possible cause of

21   subclinical PA, further supported the concept of a continuous spectrum of autonomous

22   aldosterone secretion, from subclinical forms towards overt PA. In this review we describe

23   the main aspects of LRH, focusing on molecular basis, clinical risk profile and patients'

24   management.

(A) Introduction

High blood pressure level is the most important risk factor for cardiovascular disease (1) and the leading risk factor of the global burden of disease in 2017, accounting for 10.4 million of deaths worldwide (2). Its prevalence is increasing in both low-income and high-income countries, along with an increase in lifetime expectancy (3).

Patients with arterial hypertension can be classified in three groups according to direct renin or plasma renin activity (PRA): low, normal and high renin hypertension (4). Cut-offs used to define low renin hypertension (LRH) are not strictly defined, however PRA is generally considered suppressed below 0.65-1 ng/ml/h and direct renin below 15μU/mL (5). LRH accounts for about one third of the patients with arterial hypertension (6*), with higher prevalence among elderly and patients of black African origin (7,8). New insights from clinical and preclinical studies recently expanded the spectrum of low renin phenotype towards patients without hypertension, providing clues on the progressive increase of cardiovascular risk in this particular subgroup of patients (9*).

(A) Historical background

The role of renin-angiotensin-aldosterone system (RAAS) in the pathophysiology of arterial hypertension has been investigated since 1960s, particularly by the group of John H. Laragh from Columbia University (10–12). Brunner et al., in 1972, classified arterial hypertension according to RAAS profile in a group of 219 patients (13). Comparing PRA to the nomogram drawn from normotensive individuals, they identified three subgroups of patients: 30% with

subnormal PRA, 60% with normal PRA and 10% with elevated PRA. Patients with low-renin activity displayed a lower risk of cardiovascular events, comprising stroke and myocardial infarction, despite similar blood pressure levels and cardiac organ damage. The authors concluded that low PRA could be considered a protective factor in patients with arterial hypertension (13).

One year later, Buhler FR et al. (14) further divided the low renin hypertensive group according with the response to oral sodium loading. One group displayed normal sodium-induced decrease of aldosterone levels; a second group displayed persistently unsuppressed serum aldosterone despite sodium administration. The features of the second group of patients were similar to those of patients with autonomous aldosterone secretion due to adrenal adenoma, suggesting a continuum of autonomous aldosterone secretion between low-renin essential hypertension (LREH) and PA.

In contrast with these findings, several subsequent studies reported an inverse relationship between PRA levels and blood pressure (15,16). PRA was significantly lower in patients with previous myocardial infarction than in patients without cardiac disease, suggesting increased cardiovascular risk in patients with a low-renin phenotype (15).

The pathogenesis of LRH has been debated for many years and volume expansion was the most accepted hypothesis. Many causes of volume overload have been proposed, including renal sodium retention, genetical predisposition and high sodium intake. Additionally, some authors hypothesized the presence of an unidentified mineralocorticoid hormone as the responsible of the hypervolemic state in these patients (17).

(A) Renin-angiotensin-aldosterone system and arterial hypertension

In the PATO study, among 1672 patients with hypertension, 34% displayed low-renin, 57% normal-renin and 9% high-renin hypertension (6*), confirming the data reported by Brunner et al. 35 years before (13). After exclusion of patients with PA, 75% of LREH patients had a negative screening test for PA and 25% a positive screening test and negative confirmatory test (6*).

The most frequent cause of high renin hypertension is drug interference, including diuretics and RAAS inhibitors. Even patients with PA can have high or very high renin-level during medical treatment with mineralocorticoid receptor (MR) antagonist (18). High renin levels are present in some secondary forms of hypertension: renovascular hypertension, pheochromocytoma, oral contraceptive assumption and the extremely rare juxtaglomerular renin-secreting tumors (19).

LRH is a heterogenic group of disorders, including common acquired secondary forms and rare monogenic forms. Drug treatments are commonly associated with low renin values, including nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitor and beta-blockers. High-salt diet can cause LRH by inhibiting renin activity and aldosterone secretion (18). High doses of licorice intake can cause LRH by glycyrrhetinic acid inhibition of 11BHSD2 and consequent cortisol activation of MR. Grapefruit, containing endogenous glycyrrhetinic acid like factors, may cause LRH by similar mechanism (20*). Since renin is secreted in the nephrons by juxtaglomerular cells, several renal diseases (e.g. diabetic nephropathy) may cause LRH by direct reduction of renin secretion (21).

Excluding familial forms of PA, monogenic forms of LRH display a low-renin/low-aldosterone pattern: Liddle syndrome (22), apparent mineralocorticoid excess syndrome (AME) (23), congenital adrenal hyperplasia (24) and other extremely rare disorders, including activating mutation of MR (25) and glucocorticoid resistance syndrome (26). Finally, Gordon

96   syndrome, also known as pseudohypoaldosteronism type 2, is a monogenic form LRH with

97   low or normal aldosterone levels and hyperkalaemia (27).

98   Low renin essential hypertension (LREH) is considered the most common cause of LRH.

99   However, LREH is a diagnosis of exclusion and the exact pathophysiology of LREH has yet

100   to be determined. In most cases, multiple acquired and congenital factors may play a complex

101   and synergic role (28).

102   LREH is more common in the elderly and in black African individuals (7,8). Several studies

103   have demonstrated that mild or "non-classical" monogenic form of LRH may be associated

104   with low-renin in patients with hypertension (4). Recent clinical and preclinical studies

105   demonstrated that subclinical form of PA may be comprised in this group of patients and

106   therefore, the borderline between LREH and PA became of difficult definition (29).

107   **(A) Sodium-intake and renin levels**

108   Definitions of low, normal or high sodium intake varies according to different studies and

109   institutions. World Health Organization recommend to reduce sodium-intake to less than 2

110   g/day of sodium (<5 g/day of salt) and consider an intake of more >3 g/day of sodium as

111   "high" (30). The mean dietary sodium intake worldwide is 3.7 g/day (31); according to

112   quintile distribution, sodium intake <2.6 g/day is considered low and >4.8 g/day is considered

113   high.

114   A large metanalysis recently reported that a reduction of sodium-intake from 4.6 g/day to 1.5

115   g/day, increase PRA of 1.60 ng/mL/h (55%) and aldosterone of 9.78 ng/dl (127%) (32). The

116   effect is more evident in patients with normotension than hypertension.

117   The increase of PRA with low-sodium diet is greater in the first month, followed by a

118   progressive trend towards baseline levels (33). The long-term effect of low-salt diet on renin-

119   angiotensin system has been described in Yanomami, in the tropical equatorial rain forest of

120   northern Brazil and southern Venezuela. Major staple of Yanomami diet are banana, plantains

121   and vegetables, rarely supplemented by game, fish and insects. At the time of the study (1975)

122   there was no substantial influence of the industrialized culture in the Yanomami dietary habits

123   and the daily intake of sodium of this population was extremely low with average urinary

124   sodium excretion of 1 mmol/day (34), compared with an average of 180 mmol/day in the

125   North American population (35*). The low sodium-intake resulted in high mean PRA (13

126   ng/mL/h) and high aldosterone urinary excretion.

127

128   **(A) Molecular basis of low-renin essential hypertension**

129   **(B) *Low-renin and normal/low-aldosterone***

130   In the presence of low renin and normal/low aldosterone profile, some rare monogenic

131   syndrome should be excluded, especially in young patients (see above). However, "non

132   classical" phenotypes of monogenic disorders can play a role in association with acquired and

133   dietary factors (28).

134   Missense SNPs of *SCNN1B* gene, whose mutations are responsible for Liddle's syndrome, are

135   described in patients with LRH. The prevalence of SNP rs1799979, resulting in the

136   substitution T594M, was reported in 5-8% of patients with hypertension of African origin,

137   associated with a low-renin profile (36,37). Similar findings were reported for the substitution

138   R563Q (38).

139   Beyond the classical presentation of AME, some mutations or SNPs of *HSD11B2* can results

140   in mild or "non classical" phenotype, according with the severity of HSD11B2 deficiency

141   (39). Two SNPs of *HSD11B2* gene were reported to be more prevalent in patients with

142   hypertension compared to normotensive control (40). The activity of HSD11B2 enzyme tend

143   to decrease with aging (41), supporting the hypothesis that a progressive HSD11B2

144   deficiency could partially justify the LRH phenotype in elderly hypertensives (4).

145   Recently, a genome-wide association study (42) of 757,601 individuals revealed 901 loci for

146   blood pressure traits, explaining 27% of estimated heritability. Functional analysis

147   demonstrated association with several loci involved in aldosterone secretion. Among these,

148   *CTNNB1* locus was found to be associated with systolic blood pressure levels. *CTNNB1*

149   encodes β-catenin, a protein mutated in 3% of aldosterone producing adenoma (APAs) and

150   involved in adrenocortical development and zonation (43). Whether some of these SNPs have

151   a role in LREH development has yet to be determined.

152   **(B) *Low-renin and normal/high-aldosterone***

153   Subclinical forms of PA are probably responsible for a large proportion of patients with

154   hypertension and low-renin and normal/high, but still suppressible with sodium loading,

155   aldosterone levels.

156   Aldosterone producing cell clusters (APCC) are non-neoplastic nodules of CYP11B2-

157   expressing cells that have been identified in normal adrenal gland of patient without PA and

158   in adrenal tissue near APAs (44). The number and total area of APCC increase with age in

159   patients without PA together with a reduction of the physiological zona glomerulosa

160   CYP11B2-expressing area (45*). Therefore, APCCs may be associated with autonomous

161   aldosterone secretion in elderly.

162   Absent biochemical response is encountered after 2% of total adrenalectomy (46*) and after

163   7% of adrenal-sparing nodulectomy (47). For this reason, some authors hypothesized that

164   lacking of biochemical response could be due to APCC persistence after surgical treatment.

165   However, Meyer et al. reported no significant differences in the numbers of APCC

166   surrounding the nodule of patients with complete and partial/absent biochemical outcome

167 (48). Instead, cortical hyperplasia was more frequent in patients with persistent PA,

168 suggesting nodular hyperplasia as the main risk factor of absent biochemical response (48).

169 Mutations in genes previously identified as drivers of aldosterone secretion in APA, were

170 observed also in APCC. The increased aldosterone production is mediated by increase of

171 intracellular calcium and *CYP11B2* transcription. Mutation in *CACNA1D*, encoding for a

172 subunit of L-type calcium channel, are the most frequent in APCC (26% to 58% of the cases)

173 (49*,50). *ATP1A1* mutations (encoding the α1-subunit of Na^+/K^+ transporters ATPase) in up

174 to 9% of APCCs (49*,50).

175 *KCNJ5* gene encode for the G protein-activated inward rectifier potassium channel 4 (GIRK4).

176 Mutations of *KCNJ5* alter the selectivity filter of the potassium channel, resulting in inward

177 Na^+ current, depolarization, Ca^{2+} entry in the cell and increased *CYP11B2* transcription (51).

178 Germline mutations of *KCNJ5* have been identified in patients with familial

179 hyperaldosteronism type III (52) and sporadic mutations in 40% of APA (53). Only one APCC

180 carrying a mutation of *KCNJ5* was identified (50).

181 It is possible to speculate that the transition from APCC to APAs is a potential mechanism

182 associated with the formation of *CACNA1D* and *ATP1A1* mutated APAs, but not with APAs

183 harboring *KCNJ5* mutations (Figure 1).

184 *KCNJ5* mutations are most common in female and young patients and they are associated

185 with higher chance of a complete clinical outcome after unilateral adrenalectomy (54–56).

186 Histologically *KCNJ5* mutated APA have zona fasciculata-like cells, whereas *ATP1A1* and

187 *CACNA1D* mutated APA cells are composed prevalently by zona glomerulosa-like cells

188 (57,58*).

189 *ATP2B3* is a gene encoding for a calcium-transporting ATPase mutated in about 1-2% of

190 APAs (59,60). Histological features of *ATP2B3* mutated APAs are similar compared to

191 *ATP1A1* and *CACNA1D* mutated APAs (57). However, no *ATP2B3* mutations has been

192 identified in APCCs.

193 Recently, some authors raised the hypothesis of the existence of APCC-to-APA transitional

194 lesions (pAATLs), composed of an outer part similar to an APCC and an inner part similar to

195 an APA (61).

196 **(A) The continuum from subclinical to overt PA**

197 Since its first description until the 1990s, PA was considered a very rare disorder with a

198 prevalence of less than 1%, characterized by drug-resistant hypertension and severe

199 hypokalemia (62). The widespread adoption of ARR and the expanded screening of PA in

200 patients with normokalaemia increased PA recognition of 5 to 15 times (63).

201 It is now accepted that PA is largely more prevalent than initially believed, 6% in unselected

202 hypertensive patients (6) and 11% in patients referred to tertiary centers (64). The prevalence

203 of PA increases with hypertension severity, with a prevalence of 12-13% in grade 3 (65) and

204 up to 20% in resistant hypertension (66). However, the prevalence of PA is not negligible

205 even in the in grade 1 hypertension or pre-hypertension, varying from 2 to 6% according to

206 patient selection and diagnostic criteria (64,67). The relative prevalence of unilateral forms

207 increases with hypertension grades: from 20% in grade 1 up to 30% in patients with grade 3

208 hypertension (6). Hypokalemia is present in 30% of patients with PA and is more prevalent in

209 unilateral PA than in bilateral forms (≈50% *vs* ≈20%) (6,64).

210 Recent studies expanded the spectrum of PA towards individuals with normotension and

211 normokalaemia, using a broad definition of autonomous aldosterone secretion. In one study

212 Markou *et al*. (68) performed fludrocortisone-dexamethasone suppression test in 100

213 normotensive individuals. In the second study, Baudrand *et al*. (8) performed an oral sodium

214 suppression test to 210 individuals with normal blood pressure levels and low-renin values. In

both cases the prevalence of autonomous aldosterone secretion was 13-14% (8,68). However, the strict application of the ES Guidelines (20) (positive screening test followed by confirmatory test), resulted in lower figures, with a prevalence of 3% (6 of 210 patients) (8).

Notably, patients with autonomous aldosterone secretion displayed increased 24-hours urinary aldosterone excretion and reduced urinary sodium-to-potassium excretion (8). The 24 hours urinary potassium excretion was increased, despite normal potassium levels. Patients recruited were relatively young and healthy. In this type of patients, natriuretic compensatory mechanisms can probably overcome the aldosterone-mediated volume overload and mask the hemodynamic effects of PA. On the other side, some extra-renal compensatory mechanisms can tackle potassium tubular wasting, that become overt when the compensatory effect get ineffective. Natriuretic compensatory mechanism is usually the first that become inefficient, resulting in rise of arterial hypertension with normokalaemia. Sometimes, potassium-sparing mechanisms exhaust firstly, more often in young females (69). In this cases hypokalemia may be present with normal blood pressure levels (70). Since subtype diagnosis was not performed in any of these studies, the proportion of normotensive patients with autonomous aldosterone secretion due to unilateral PA is unknown.

The prevalence of subclinical PA progressively increases with aging; *Nanba et al.* (45*) explored RAAS profile and aldosterone regulation in 667 patients without PA, using ARR and sodium-modulated aldosterone suppression-to-stimulation index (SASSI). SASSI is calculated as the ratio of suppressed serum aldosterone/stimulated serum aldosterone, induced by sodium-loading and sodium-restriction respectively (45*). High SASSI suggests renin-independent aldosterone secretion, whereas low SASSI suggests normal aldosterone regulation (71*); SASSI and ARR progressively increase with age independently of other confounding conditions (45*).

(A) Cardiovascular risk profile associated with subclinical primary aldosteronism

Vasan *et al.* (72*) showed the role of aldosterone as a risk factor in the development of hypertension in 1688 normotensive participants of the Framingham Offspring Study. Subjects with aldosterone levels in the highest quartile displayed 1.61-fold increased risk of hypertension. Subsequently, in the Framingham Heart Study cohort of 3326 individuals, it was shown that ARR was significantly associated with blood pressure progression and hypertension incidence (73). The authors concluded that aldosterone is a risk factor for hypertension development only when is inappropriate for renin levels.

Brown *et al.* confirmed this findings, reporting higher incident hypertension (85.4 per 1000 person/years) in patients with low renin phenotype (PRA ≤ 0.50 ng/m/h) than in patients with PRA ≥ 1.00 ng/ml/h. Serum aldosterone was significantly associated with incident hypertension only when renin activity was suppressed (18% of increased risk per 100 pmol/l of increased serum aldosterone) (35). In another study, 85% of patients with autonomous aldosterone secretion developed hypertension in the following 5 years, versus 23% in patients without autonomous aldosterone secretion (68). It is currently unknown whether the risk of developing overt PA is increased in patients with subclinical PA.

It is uncertain if patients with subclinical PA or mild PA have an increased risk of cardio-cerebrovascular events or metabolic disorders before the development of overt PA. A recent study, evaluating patients with both normotension or hypertension but without PA, reported a correlation of ARR with metabolic syndrome, body mass index, blood pressure levels and markers of endothelial dysfunction (74). In the PATO study, Monticone *et al.*, compared a large group of 464 patients with LREH and 1109 patients with normal or high PRA: patients in the LREH group displayed higher blood pressure levels but no significant differences in terms of metabolic disorders, cardiovascular events or target organ damage (6). Similarly, in the study

264 of Markou *et al.* normotensive patients with autonomous aldosterone secretion display similar

265 metabolic profile compared with patients with normal aldosterone secretion (68).

266

267 **(A) Future perspectives in PA diagnosis**

268 The existence of an expanding horizon of PA towards mild and subclinical forms raise several

269 questions on the optimal and cost-effective approach for PA diagnosis.

270 In order to maximize PA recognition, *Vaidya et al.* (9) recently suggested to loosen the criteria

271 to define positive the screening test for PA. They proposed to consider PA diagnosis even in

272 patients with aldosterone in normal range (5-10 ng/dl) and suppressed renin levels, suggesting

273 to repeat the screening test or directly performing a confirmatory test in these patients.

274 Using wider criteria for PA diagnosis would increase costs for PA diagnosis and subtype

275 differentiation. A part of this cost may be covered by the reduced risk of cardiovascular events

276 in these patients.

277 At the same time, no study directly investigated the prevalence of APAs in subclinical PA.

278 Therefore, whether patients with subclinical PA should undergo a complete subtype diagnosis

279 is another unmet issue. Adrenal venous sampling (AVS), the current gold standard for subtype

280 characterization (20), is an expensive and invasive technique. Therefore, performing a complete

281 subtype diagnosis for an increasing number of patients could be challenging even for

282 specialized centers. Scoring system or laboratory tests, aimed at identifying patients with a low

283 probability of having unilateral PA may be of help in reducing the number of procedures.

284 Patients with low probability of APAs, could probably avoid further invasive procedures and

285 benefit of specific treatment with MR antagonist (9).

286 Finally, it should be noted that even with the current criteria for PA, the large majority of

287 patients with PA remain undiagnosed (75*). Therefore, widening the criteria for PA without

288 an effort for an improvement in PA awareness would probably solve just a part of the

289 problem.

290

291 **(A) Summary**

292 Low renin hypertension is highly prevalent condition in individuals with arterial hypertension,

293 involving one third of the patients. The causes of LRH comprise rare monogenic forms of

294 hypertension and more common acquired forms, in which congenital predisposing factors

295 play a role together with acquired condition and dietary habits. The expansion of the spectrum

296 of PA supports the hypothesis that a large part of LRH, particularly if associated with normal-

297 high aldosterone levels, is probably caused by subclinical form of PA.

298 Understanding the molecular basis that underlie the pathogenesis of low renin hypertension

299 opened new unexpected areas of research. At the same time, the best diagnostic and

300 therapeutic approach for this particular subgroup of patients has yet to be determined. Future

301 studies should address these issues guiding the clinicians towards a new tailored approach of

302 the patients with arterial hypertension.

303

304 **Practice point**

305 - Low-renin hypertension (LRH) is generically defined as arterial hypertension with

306   plasma renin activity below 0.65-1 ng/ml/h or direct renin below 15μU/mL

307 - LRH account for about 35% of patients with arterial hypertension, with higher

308   prevalence among elderly and patients of African origin

309 - LRH is caused by some rare monogenic forms and most common acquired forms,

310   caused by a complex admixture of congenital predisposition and dietary and acquired

311   factors

312 - Subclinical primary aldosteronism (PA) is probably the cause of a large part LRH with

313   normal-high aldosterone levels

Research agenda

315 - Investigate the genetic variants determining the heritability of low-renin essential

316   hypertension

317 - Determine the cardiovascular risk of patients with subclinical PA, the risk of

318   development of overt PA and the prevalence of unilateral forms in subclinical PA

319 - Define the management of patients with subclinical PA in terms of diagnosis,

320   treatment and follow-up

Conflict of interest

322

Acknowledgments

324

Figure 1

326 Histopathological and clinical features of the spectrum of primary aldosteronism (PA) from

327 subclinical to overt PA. APA=aldosterone producing adenoma. IHA=idiopathic

328 hyperaldosteronism. APCC=aldosterone producing cell clusters.

329

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