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(Article begins on next page)

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.

25 **Key words:** primary aldosteronism, low renin hypertension, aldosterone producing adenoma,
26 aldosterone producing cells cluster

27 **Word count:** 5146 (including references)

28 **(A) Introduction**

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

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

42

43 **(A) Historical background**

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

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

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

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

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

70

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

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

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

83 LRH is a heterogenic group of disorders, including common acquired secondary forms and
84 rare monogenic forms. Drug treatments are commonly associated with low renin values,
85 including nonsteroidal anti-inflammatory drugs, cyclooxygenase-2 inhibitor and beta-
86 blockers. High-salt diet can cause LRH by inhibiting renin activity and aldosterone secretion
87 (18). High doses of licorice intake can cause LRH by glycyrrhetic acid inhibition of
88 11BHS2 and consequent cortisol activation of MR. Grapefruit, containing endogenous
89 glycyrrhetic acid like factors, may cause LRH by similar mechanism (20*). Since renin is
90 secreted in the nephrons by juxtaglomerular cells, several renal diseases (e.g. diabetic
91 nephropathy) may cause LRH by direct reduction of renin secretion (21).

92 Excluding familial forms of PA, monogenic forms of LRH display a low-renin/low-
93 aldosterone pattern: Liddle syndrome (22), apparent mineralocorticoid excess syndrome
94 (AME) (23), congenital adrenal hyperplasia (24) and other extremely rare disorders, including
95 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 *CACNAID*, 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 α 1-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 *CACNAID* 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 *CACNAID* 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 ($\approx 50\%$ vs $\approx 20\%$) (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

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

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

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

239

240 **(A) Cardiovascular risk profile associated with subclinical primary aldosteronism**

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

248 Brown *et al.* confirmed this findings, reporting higher incident hypertension (85.4 per 1000
249 person/years) in patients with low renin phenotype ($PRA \leq 0.50$ ng/ml/h) than in patients with
250 $PRA \geq 1.00$ ng/ml/h. Serum aldosterone was significantly associated with incident hypertension
251 only when renin activity was suppressed (18% of increased risk per 100 pmol/l of increased
252 serum aldosterone) (35). In another study, 85% of patients with autonomous aldosterone
253 secretion developed hypertension in the following 5 years, versus 23% in patients without
254 autonomous aldosterone secretion (68). It is currently unknown whether the risk of developing
255 overt PA is increased in patients with subclinical PA.

256 It is uncertain if patients with subclinical PA or mild PA have an increased risk of cardio-
257 cerebrovascular events or metabolic disorders before the development of overt PA. A recent
258 study, evaluating patients with both normotension or hypertension but without PA, reported a
259 correlation of ARR with metabolic syndrome, body mass index, blood pressure levels and
260 markers of endothelial dysfunction (74). In the PATO study, Monticone *et al.*, compared a large
261 group of 464 patients with LREH and 1109 patients with normal or high PRA: patients in the
262 LREH group displayed higher blood pressure levels but no significant differences in terms of
263 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 15 μ U/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

314 **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

321 **Conflict of interest**

322 Paolo Mulatero received fees for educational speech from DIASORIN.

323 **Acknowledgments**

324 None

325 **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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