Quality of Life in Patients with Bilateral Primary Aldosteronism before and during Treatment with Spironolactone and/or Amiloride, Including a Comparison with Our Previously Published Results in Those with Unilateral Disease Treated Surgically

Endocrine Hypertension Research Centre, University of Queensland School of Medicine, Greenslopes and Princess Alexandra Hospitals, Brisbane 4102, Australia

Background: Measurement of quality of life (QOL) allows assessment of the impact of a disease or treatment from the patient’s perspective, including need for social, emotional, or physical support. We are not aware of any published QOL assessment in patients with bilateral primary aldosteronism (BPA), before or after commencing medical treatment (MT) with spironolactone and/or amiloride.

Methods: Using the internationally validated Medical Outcomes Study Short Form 36 General Health Survey (SF-36), QOL was assessed in 21 patients with BPA at baseline (time of diagnosis), and at 3 and 6 months after commencing MT. QOL scores at baseline were compared with published normative values for the Australian population. The results of the current study were compared with those from our previous study showing reduced QOL in patients with unilateral primary aldosteronism (UPA) with normalization by 3 months after unilateral laparoscopic adrenalectomy.

Results: Compared with the general population, patients with BPA showed significant reduction ($P < 0.01$) in four QOL domains—physical functioning, role limitations due to physical health problems, general health perceptions, and vitality. After 6 months (but not 3 months) of MT, statistically significant ($P < 0.05$) improvements were detected in all these domains of QOL. When compared with patients with UPA treated surgically, scores were significantly ($P < 0.05$) lower at 3 months for five domains (role limitations due to physical health, general health, role limitations due to emotional health, mental health, and vitality) but at 6 months for only one domain (role limitations due to emotional problems).

Conclusion: Subnormal QOL scores were improved after 6 months of MT in 21 patients with BPA, but more slowly and to a lesser degree than surgical treatment had previously been shown to improve QOL scores in 22 patients with UPA. (J Clin Endocrinol Metab 96: 2904–2911, 2011)
vascular events (4) and renal dysfunction (5) than subjects with “essential” hypertension matched for blood pressure levels. Unilateral laparoscopic adrenalectomy leads to cure of hypertension in 50–60% of patients with unilateral PA and improvement in virtually all remaining patients (6). On the other hand, treatment with spironolactone usually brings about marked improvement in hypertension control (7) in patients with bilateral forms. Both forms of treatment have been reported to abrogate the excess in cardiovascular and renal morbidity that otherwise occurs when patients with PA are treated with nonspecific antihypertensive medications (8).

Measurement of disease status alone, such as size of myocardial infarction, tumor load, or severity of hypertension, has been recognized by health care planners as an insufficient determinant of health status (9, 10). Other psychosocial factors such as pain, restricted mobility, difficulty fulfilling personal and family responsibilities, and financial burden should be considered in assessing the personal burden of illness (10). Consequently, measurement of health-related quality of life, otherwise known as quality of life (QOL), has emerged as a complementary health status measure (9). The term QOL refers to the physical, psychological, and social domains of health, seen as distinct areas that are influenced by a person’s experiences, beliefs, expectations, and perceptions (11). Measurement of QOL considers the impact of the disease or its treatment from the patient’s perspective (12) and determines the need for any support during illness, including social, emotional, and physical support. We previously reported that QOL was significantly reduced below Australian norms in patients with unilateral PA but was significantly improved to normal levels within 3 months after unilateral adrenalectomy, with this improvement being maintained at 6 months (13). We are unaware of comparable published data regarding QOL assessment in patients with bilateral PA before and after commencing medical treatment.

Psychosocial factors have been insufficiently explored in PA. PA has been reported to be associated with depression (14–16). In a study conducted by Sonino et al. (17) to investigate the presence of psychiatric disorders and subclinical psychological syndromes in newly diagnosed PA patients, seven of 10 patients were found to have anxiety disorder, with one also having major depression. Demoralization was reported in five cases. In that study, a chance association between these psychological disorders and PA cannot be excluded because of the small sample size. Whether the psychological distress preceded or followed the onset of aldosteronism could not be determined, but it does seem much more likely to have followed it. Recent studies in rats have shown that administration of aldosterone leads to increased anxiety-like behavior (18), and the selective mineralocorticoid receptor blocker, eplerenone, has anxiolytic effects (19).

The present study was designed to: 1) evaluate various physical and psychological aspects of QOL in patients with bilateral PA before and after commencing medical treatment with amiloride and/or spironolactone using the Medical Outcomes Study Short Form 36 General Health Survey (SF-36) (20); and 2) compare the outcome of the current study with the results of the earlier study performed by our group to evaluate the effect of unilateral laparoscopic adrenalectomy on QOL in patients with unilateral PA (13). Two medications that antagonize the sodium-retaining effect of aldosterone on the sodium epithelial channel in the renal collecting duct were employed: spironolactone, which also opposes actions of aldosterone on the heart and cardiovascular system (21); and amiloride, which is thought not to share this property, but presumably opposes aldosterone action wherever the sodium epithelial channel operates, as in sweat and salivary ducts and the large intestine. We employed amiloride alone or in combination with spironolactone to avoid or reduce the dose-dependent antiandrogen effects of spironolactone.

Subjects and Methods

Subjects

This study was completed between January 2009 and December 2010 in the Endocrine Hypertension Research Center, Greenslopes and Princess Alexandra Hospitals, Brisbane, Australia. The diagnosis of PA and its subtype was based on the center’s strict protocol (22). All patients had screened positive by aldosterone/renin ratio (ARR) measured off interfering medications; PA was confirmed by fludrocortisone suppression testing and bilateral PA by adrenal venous sampling. The institutional ethics committee approved the study. Patients were informed of the objectives of the study, and informed consent was obtained in all cases. The 21 medically treated patients who completed the study comprised 14 females (mean age, 55.3 ± 9.8 yr; mean weight, 77.9 ± 16.9 kg) and seven males (mean age, 52.8 ± 9.0 yr; mean weight, 102.5 ± 21.3 kg) with a combined mean age of 54.5 ± 9.4 (range, 34–75) yr and a combined mean weight of 86.1 ± 21.6 (range, 52–145) kg. Ten patients received spironolactone at doses ranging from 12.5 to 25 mg/d, and nine patients received amiloride at doses of 2.5 to 10 mg/d. Two patients received both medications (within similar dose ranges to the others). As is our usual empirical practice, renin levels were monitored as a guide to adequacy of dosage of amiloride and/or spironolactone in opposing excessive reabsorption of sodium in the renal collecting duct. Renin becoming unsuppressed and rising into the normal range was regarded as being suggestive of adequate dosage; renin levels rising above normal suggested excessive dosage and was followed by further elevation of aldosterone.

Measurement of plasma aldosterone and renin

Plasma aldosterone and renin were measured midmorning, after 2–4 h upright at baseline (after diagnosis of bilateral PA),
and once between 3 and 6 months after commencing medical treatment with amiloride and/or spironolactone. Plasma renin concentration was determined by direct renin assay, which uses chemiluminescent immunoassay technology (Liaison; DiaSorin, Saluggia, Italy). The interassay coefficient of variation was 7.4% at 26 mU/liter and 6.0% at 106 mU/liter. The intraassay coefficients of variation at 15, 33, 82, and 258 mU/liter were 3.7, 2.8, 2.0, and 1.2%, respectively. The assay working range was up to 500 mU/liter. Plasma aldosterone concentration was measured by solid-phase RIA technique using Coat-A-Count assay (Diagnostic Products Corporation, Los Angeles, CA). The interassay coefficients of variation at 98, 631, and 1458 pmol/liter were 15, 6, and 6%, respectively. The intraassay coefficient of variation was 2.3–5.4% for values in the range 180–2256 pmol/liter. The midmorning upright normal range for renin for subjects on a liberal sodium diet is 8–34 mU/liter and for aldosterone is 140–1100 pmol/liter.

**Assessment of QOL**

QOL was measured at baseline and 3 and 6 months after commencing medical treatment by the SF-36, a generic questionnaire internationally validated in the general population (23). It is a written, self-administered questionnaire, and it has been previously validated in Australia (24). The SF-36 can be scored as eight subscales. Each scale score is constructed from a varying number of items. These are physical functioning (10 items), social functioning (two items), role limitations due to physical problems (four items), role limitations due to emotional problems (three items), vitality (four items), bodily pain (two items), general health perceptions (five items), and general mental health (five items). Scores range from 0 (poorest health status) to 100 (best health status) (20). Results were compared with published normative values for the Australian population.

**Demographic and clinical data**

Demographic and clinical data recorded included blood pressure, medications, plasma upright aldosterone and renin concentrations, ARR, and plasma potassium and sodium levels at baseline and once between 3 and 6 months after medical treatment. For each patient, the spironolactone and/or amiloride treatment was included in the number of medications recorded after commencement of treatment.

Outcomes in the current study of bilateral PA were compared with those in our study of unilateral PA previously reported (13).

**Statistical analysis**

The data were analyzed using SPSS 17.0 for Windows (SPSS Inc., Chicago, IL). All values are expressed as mean ± SD unless otherwise specified. ANOVA was used for multiple comparisons between baseline, 3-, and 6-month results of SF-36 scores. Pairwise comparisons of SF-36 scores, blood pressure, and biochemical parameters were performed using paired t test. Comparison of SF-36 scores with published normative values for the Australian general population was performed using t test. Comparison of the effects of medical treatment of bilateral PA with surgical treatment of unilateral PA was performed by t test. Statistical significance was accepted when the two-tailed P value was <0.05.

**Results**

**Biochemical and hemodynamic data**

**Changes after medical treatment**

As shown in Table 1, within 3 to 6 months after medical treatment, both mean systolic blood pressure (SBP) and
mean diastolic blood pressure (DBP) had significantly improved (baseline SBP, 166.0 ± 19.2 mm Hg, P < 0.001; and DBP, 100.0 ± 8.3 mm Hg, P < 0.001) (Fig. 1). Although the number of antihypertensive agents (amiloride and spironolactone included) did not change significantly (2.57 ± 0.13 vs. 2.47 ± 0.16), plasma potassium levels significantly increased (3.75 ± 0.36 vs. 4.08 ± 0.26 mmol/liter, P = 0.001). Hypokalemia, present in four patients at the time of diagnosis, was corrected in each case. Plasma sodium levels decreased slightly but significantly (140.8 ± 2.3 vs. 138.6 ± 2.6 mmol/liter; P = 0.004). Mean upright renin concentration (2.71 ± 0.84 vs. 8.42 ± 1.16 mU/liter; P < 0.001) rose significantly but remained within the normal range. Plasma aldosterone (411.4 ± 90.3 vs. 513.8 ± 94.1 pmol/liter; P < 0.001) also rose significantly within the normal range, but the rise in renin was greater than the rise in aldosterone, leading to a significant reduction in mean ARR (158.0 ± 34.1 vs. 60.9 ± 7.3; P < 0.001).

**Comparisons between medical and surgical treatments**

Table 1 shows comparisons of blood pressure and biochemical parameters in patients with bilateral PA who were treated medically with those in patients with unilateral PA treated by unilateral laparoscopic adrenalectomy [taken from Sukor et al. (13)]. At baseline, patients with bilateral PA had similar blood pressure levels and were on similar numbers of antihypertensive medications. Patients with bilateral PA had lower plasma aldosterone and ARR levels and higher plasma potassium levels than those with unilateral PA.

Three to 6 months after surgery or commencement of medical treatment, DBP was significantly higher in medically treated patients (86.0 ± 0.8 vs. 80.0 ± 1.6 SEM mm Hg; P < 0.01), and SBP tended to be higher in medically treated patients, but the difference did not quite reach statistical significance (P = 0.063). As expected, the number of antihypertensive agents employed was significantly higher in the medically treated group (2.47 ± 0.16 vs. 0.10 ± 0.06; P < 0.001). The mean falls in SBP, DBP, and number of antihypertensive medications after surgery or commencement of medical treatment, respectively, were all greater (P < 0.05) in surgically treated patients than in the medically treated group. The medically treated patients had similar renin levels (8.42 ± 0.25 vs. 6.80 ± 1.20 mU/liter; P > 0.05) to those of the surgically treated group but, as expected, higher levels of aldosterone (513.8 ± 20.5 vs. 128.8 ± 24.8 pmol/liter; P < 0.001), and ARR (60.9 ± 1.6 vs. 23.0 ± 4.7; P < 0.001) in association with significant (P ≤ 0.001) rises in both renin and potassium levels, both of which are predictable outcomes of aldosterone antagonism that should lead to increased aldosterone secretion. As a result, ARR levels also fell to a greater degree in surgically treated patients.

**SF-36 scores**

**Changes after medical treatment**

At baseline, the scores were significantly lower for patients with bilateral PA than that reported for the Australian general population in four domains (Table 2): physical functioning (72.4 ± 15.5 vs. 87.4 ± 19.7; P < 0.001), role limitations due to physical health problems (57.1 ± 32.7 vs. 84.5 ± 31.9; P < 0.001), general health perceptions (60.4 ± 9.5 vs. 73.8 ± 19.2; P < 0.01), and vitality (52.3 ± 15.2 vs. 65.6 ± 19.0; P < 0.01).

Mean scores obtained from SF-36 domains before medical treatment and after 3 and 6 months of treatment are shown in Table 2 and Fig. 2. At 3 months, there were no significant changes in any domain, compared with baseline, but by 6 months after treatment commenced, scores for physical functioning (baseline, 72.4 ± 15.5 vs. 79.7 ± 10.1; P = 0.001), role limitations due to physical health problems (57.1 ± 32.7 vs. 73.8 ± 18.5; P < 0.05), general health (60.4 ± 9.5 vs. 72.0 ± 9.9; P < 0.001), and vitality (52.3 ± 15.2 vs. 60.9 ± 17.0, P < 0.01) had significantly increased. As a result, the scores in each of these four domains, although significantly lower than that reported for the general population at baseline and at 3 months, rose to reach those of the normal population scores by 6 months.

**Comparison of medical and surgical treatments**

Comparison of the effects of medical treatment of bilateral PA vs. the effects of unilateral laparoscopic adre-
nalectomy in patients with unilateral PA on QOL is shown in Table 3. There were no significant differences in the scores of any domain of QOL between the two groups at baseline. The scores improved dramatically 3 months after surgery but not 3 months after medical treatment. As a result, at 3 months, the scores were higher (P < 0.05) among the surgically treated group than the medically treated group for five domains (role limitations due to physical health problems, general health, role limitations due to emotional problems, mental health, and vitality). However, by 6 months, only the scores for role limitations due to emotional problems were lower in the medically treated group (76.1 ± 21.4 vs. 92.4 ± 20.4; P < 0.05).

**Discussion**

This study reports, perhaps for the first time, statistically significant improvement in four domains of QOL (physical functioning, role limitations due to physical health problems, general health, and vitality) after 6 months of starting medical treatment of bilateral PA with spironolactone and/or amiloride. The current study suggests that medical treatment of PA with these agents, which oppose aldosterone action in the renal collecting duct, has a positive impact not only on blood pressure and biochemical parameters but also on QOL. This further supports the value of detecting and treating this common cause of hypertension early and with appropriate agents.

In the present study, there were no significant changes observed in any domain of QOL 3 months after commencing medical treatment, whereas the previous study of surgical treatment in patients with unilateral PA (13) demonstrated significant, early QOL improvement, with...
scores in each of the eight domains rising to normal by 3 months after surgery; that is a faster and more profound effect on QOL for surgical than medical treatment.

Why would surgery achieve faster and more complete correction of reduced QOL scores? Surgically removing the source of aldosterone excess is clearly faster and might also be more complete than attempted reversal of excessive mineralocorticoid action. We attempted to avoid inadequate dosage by monitoring renin levels, and these were not suppressed compared with the surgically treated patients. We avoided failure to achieve optimal dosage because of side effects such as gynecomastia by using amiloride alone or in combination with spironolactone, thus avoiding this dose-related side effect. Careful, regular follow-up made poor compliance in the medically treated patients unlikely.

Mechanisms by which QOL might be reduced in subjects with PA include nonspecific symptoms of hypertension, adverse effects of antihypertensive medications, and symptoms of aldosterone excess including those due to reduced potassium (palpitations, neuromuscular symptoms, and nocturia) and possibly obstructive sleep apnea [reported to be more frequent in PA than in other forms of hypertension (25, 26)]. Sukor et al. (13) suggested that correction of hypokalemia after treatment of PA is a possible mechanism by which treatment can improve QOL because hypokalemia can cause muscle weakness, cramps, paresthesias, polyuria, and nocturia. The expected increase in mean plasma potassium level during medical treatment was seen in the present study, with correction of hypokalemia in the four patients with hypokalemia at the time of diagnosis. Only a minority of patients with PA have hypokalemia (27), more commonly in patients with aldosterone-producing adenoma than in those with bilateral adrenal hyperplasia (28). Improvement in control of hypertension by spironolactone and/or amiloride in the present study may have contributed to the improvement in QOL.

Aldosterone excess may bring about disturbances in psychological function (including mood and anxiety disorders) through central mechanisms. Depression is associated with many symptoms that significantly affect QOL, including melancholic mood, loss of interest or pleasure, fatigue, sleep disturbances, and agitation (29). Increased plasma aldosterone levels have been reported in patients with depression (30, 31), and there have been several case reports of PA presenting with depression. Anxiety has a negative impact on QOL (32), and chronic treatment with aldosterone in rats caused anxiety-like behavior (18), whereas administration of eplerenone, a mineralocorticoid receptor blocker, was observed to exert anxiolytic effects (19). Pharmacological blockade of the renin-angiotensin system by angiotensin II receptor blockers or angiotensin-converting enzyme inhibitors with reduction in aldosterone levels has been reported to improve mood and have anxiolytic effects in man (33, 34). Treatment with angiotensin II receptor blockers in rats also has anxiolytic effects (35–37) and reduces plasma aldosterone (38). Hence, considerable evidence from both clinical and experimental studies supports relationships between aldosterone and mood disorders, with improvement when aldosterone effects are opposed by medications.

How may aldosterone exert such central effects to bring about these psychological disturbances? 1) Aldosterone can stimulate activation of proinflammatory cytokines (39, 40). Continuous iv infusion over 24 h of human
TNF-α, a cytokine, was reported to induce depressive symptoms such as fatigue, malaise, lethargy, and irritability in human subjects (41). Therapeutic administration of the cytokine interferon-α (IFN-α) for clinical treatment of malignant melanoma has been found to cause depression (42), but we are unaware of any studies examining effects of aldosterone excess on IFN-α levels. IFN-α-induced depression is responsive to treatment with standard antidepressants (42, 43). Depressed patients have been found to have higher levels of proinflammatory cytokines (43). 2) Aldosterone causes salt and water retention, and salt-sensitive individuals have been shown to complain from increased levels of irritability, higher levels of anxiety, and lower levels of anger control (44, 45). 3) Injection of mineralocorticoid receptor antagonists into the brains of rats has been shown to induce anxiolytic effects (46–48). However, consideration of central nervous system effects of aldosterone needs to be taken in the context of its very high reflection coefficient at the blood-brain barrier and the very limited central nervous system expression of 11-β hydroxysteroid dehydrogenase type II which, in other tissues where it is more abundant, serves to “protect” the mineralocorticoid receptor from binding by cortisol by converting this hormone into cortisone (49).

Although QOL is difficult to measure and there is no consensus on the single best instrument to use, a strength of this study is the use of internationally validated SF-36 questionnaires. The SF-36 Health Survey has emerged as being the most widely used generic instrument for measuring perceived health status in various diseases and conditions. A second strength was availability of a group of bilateral PA patients carefully and uniformly investigated at Greenslopes and Princess Alexandra Hospitals using strict criteria for the diagnosis of PA, including accurate differentiation of unilateral from bilateral. Thirdly, to our knowledge, this is the first study to be performed to evaluate the effect of medical treatment of bilateral PA on QOL. An important limitation of the study, however, is the lack of a control group consisting of hypertensive patients without PA after commencement of antihypertensive medication, either nonspecific or using aldosterone blockade. In further subgroups of PA patients, the effects on QOL of various treatments could be examined (but with difficulty due to small numbers available), for example, by examining effects of unilateral adrenalectomy in patients with bilateral PA and of aldosterone antagonist treatment in patients with unilateral PA who are unsuitable for or who decline surgery. The effect of spironolactone and amiloride on QOL could be assessed in patients with resistant hypertension (where their use has been recommended (50) in whom PA had been excluded. This might help to disentangle the influences of these medical-

tions and the achieved lowering of blood pressure on QOL in the absence of autonomous, excessive aldosterone action.

In conclusion, QOL scores were lower in bilateral PA patients than reported for the Australian general population, and medical treatment was associated with a positive effect on QOL. Early detection of PA is crucial, not only because treatment minimizes the complication of long-term exposure to aldosterone excess and brings about marked improvement in hypertension control, but also because it improves QOL. Comparison with QOL results in a cohort with unilateral PA treated surgically showed a faster and more complete recovery of QOL in the latter group.

Acknowledgments

Address all correspondence and requests for reprints to: Prof. Michael Stowasser, Endocrine Hypertension Research Centre, University of Queensland School of Medicine, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane 4102, Australia. E-mail: m.stowasser@uq.edu.au.

This work was funded by the University of Queensland Irene Patricia Hunt Memorial Trust for Hypertension Research. A.H.A. was supported by an educational grant from the Iraqi Ministry of Higher Education.

Disclosure Summary: The authors have nothing to disclose.

References

chomeric properties and results of the international field trial. A report from the WHOQOL group. Qual Life Res 13:299–310
18. Hlavacova N, Jezova D 2008 Chronic treatment with the mineralocorticoid hormone aldosterone in increased anxiety-like behavior. Horm Behav 54:90–97
23. McHorney CA, Ware Jr JE, Raczek AE 1993 The MOS 36-Item Short Form Health Survey (SF-36). II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. Med Care 31:247–263