INVITED REVIEW

Cardiovascular complications of Cushings syndrome: Impact on morbidity and mortality

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1 INTRODUCTION

Patients with Cushing’s syndrome have increased morbidity and mortality from cardiovascular causes, most commonly myocardial infarction and stroke, but also aneurysms and pulmonary emboli.1,2 These are also common causes of death in the general population in developed countries and are age-dependent. It has been estimated that untreated Cushing’s syndrome patients have a four- to five-fold higher mortality rate than the general population, with only 50% of patients surviving 5 years from diagnosis.3 The 5-year survival rate was improved to 86% after bilateral adrenalectomy.4 The major risk factors for this mortality in the general population are diabetes (DM2), hypertension, smoking, dyslipidaemia, abdominal obesity/metabolic syndrome, and male gender. These same risk factors pertain in all forms of glucocorticoid excess. Here, I focus on endogenous Cushing’s syndrome and pertinent to this is that the majority of patients (70%–80%) have adrenocorticotrophic hormone (ACTH)-dependent pituitary Cushing’s disease and are frequently women (75% of cases) of premenopausal age, typically between 30 and 55 years old at diagnosis. This sex and age-group has a low incidence of cardiovascular disease in the general population. Furthermore, Cushing’s syndrome patients are exposed to excess glucocorticoid for approximately 3–4 years before diagnosis and effective treatment, thereby increasing the likelihood of early development of cardiovascular risk factors. Even more concerning is the fact that, even after ‘cure’ of the Cushing’s syndrome, the risk factors may not fully normalise with adequate amelioration of glucocorticoid excess.

The present review aims to briefly delineate the major cardiovascular complications of endogenous Cushing’s syndrome as they relate to the heart, vasculature, and hypertension. I examine the evidence for the reversibility of these changes, particularly over the long-term (> 1 year), as well as how these factors relate to cardiovascular events and mortality. This is particularly important as long-term ‘cure’ of Cushing’s disease may be associated with near-normal life-expectancy because younger patients may expect to live for 30–40 years after diagnosis and curative treatment.5 In this review, ‘cure’ is taken to mean ‘restoration of eucortisolaemia’ as defined by the authors of the publications, which use variable criteria, and those that were commonly accepted at the time of their publication. It does not necessarily equate to normalisation of metabolic risk factors. Treatments used were predominantly surgical but may have included other modalities (for details, see individual studies).

2 CARDIAC CHANGES IN CUSHING’S SYNDROME

Table 1 shows some of the literature regarding the main changes that have been observed in the heart over the last 20 years using various echocardiographic modalities. This is by no means exhaustive, but is representative. These changes are separate from the increased left ventricular mass index and the concentric left ventricular hypertrophy that accompanies hypertension. Although many studies have demonstrated left ventricular remodelling, fewer have examined the effect of this on left ventricular function.

The study by Muiesan et al6 compared 42 patients with Cushing’s syndrome with the same number of controls matched for age, gender, and blood pressure. In the patients, left ventricular relative wall thickness was greater and midwall fractional shortening was reduced compared to controls. Both of these factors led to reduced systolic performance and diastolic dysfunction and appear to be cortisol specific because the same changes were observed in normotensive patients versus normotensive controls. Although these features have been linked as risk factors for cardiovascular disease in the general population, it is not clear whether they necessarily contribute to the increased morbidity and mortality seen in Cushing’s syndrome.
population, there is no such link demonstrated for Cushing's syndrome. There are no post-treatment data in this report. Moreover, in the study, there is no mention of clinical cardiac symptoms in the cohort.

In a later echocardiographic study, Toja et al found that parameters of left ventricular mass and relative wall thickness significantly improved 1 year after 'cure', although they were still greater than in controls. Subtle left ventricular systolic dysfunction reversed and diastolic function was normal.

In a small group (n = 15) of Cushing's syndrome patients investigated by Periera et al using two-dimensional speckle strain imaging, left ventricular diastolic dysfunction remained significantly lower than in controls after multivariate analysis with body mass index and left ventricular mass index as covariates. At 12–18 months after resolution of hypercortisolaemia, these changes resolved. Speckle strain imaging allows left ventricular mechanical properties to be tracked in real time in three dimensions along the cardiac cycle, giving more detail of functional changes. No information on clinical features of heart disease was provided. A follow-up report on the same patients by Yiu et al using calibrated integrated backscatter, demonstrated increased myocardial fibrosis that was significantly related to left ventricular systolic and diastolic function. This reversed after 'cure' but, again, there was no mention of clinical cardiac function resulting from these changes.

Using cardiac magnetic resonance imaging, Kamenicky et al showed that left ventricular, right ventricular, and left atrial ejection fractions were lower and end-diastolic left ventricular segmental thickness increased compared to controls. All of these features improved 2–12 months after resolution of hypercortisolaemia.

**TABLE 1**  
Cortisol specific changes in the heart

| Study authors (year) | Reference | Essential findings | Changes on resolution of Cushing's syndrome |
|----------------------|-----------|-------------------|-------------------------------------------|
| Mulesan et al (2003) | 6         | 26/42 patients: 1 or > of increased left ventricular relative wall thickness/midwall fractional shortening causing reduced systolic and diastolic function | No measurements |
| Periera et al (2010) | 7         | 15 CD vs. 30 controls with left ventricular hypertrophy causing reduced systolic and diastolic function | Reversed after 12–18 months |
| Yiu et al (2012)     | 8         | Same patients as in reference 7, integrated back scatter showing increased myocardial fibrosis | Reversed after 12–18 months |
| Toja et al (2012)    | 9         | 49 active CD; 44 cured CD; 70 control indices of left ventricular mass higher in both CD groups with blood pressure increased; subtle left ventricular systolic function and diastolic function normal in 90% | Improved 4–48 months reversed in cured pts; |
| Kamenicky et al (2014)| 10        | Cardiac magnetic resonance imaging in 18 patients vs. 18 controls: left ventricular, right ventricular, and left atrial ejection fractions reduced | Resolved 2–12 months |
| Frustaci et al (2019)| 11        | Eight of 473 patients CD as a result of adrenal adenoma that had hypertrophied hypokinetic left ventricular ejection fraction < 30%. Myocyte cell diameter, myocardial fibrosis, and myofibrillolysis area are all increased; high levels of atrogin-1 mRNA and protein reduced significantly after adrenalectomy | Resolved/improved |

Abbreviations: CD, Cushing's disease.

Dilated cardiomyopathy (DCM) with severe left ventricular failure is rare in Cushing's syndrome. However, a study by Frustaci et al found eight cases of Cushing's syndrome as a result of adrenal adenoma in 473 patients with DCM (1.7%). These patients all had left ventricular ejection fractions < 30% and symptoms of heart failure. Endomyocardial biopsies were performed pre-treatment and on three of eight patients 1 year after adrenalectomy. Biopsies showed increased myocyte diameter, myocardial fibrosis, and myofibrillolysis area compared to subjects with idiopathic DCM and controls with valvular heart disease without heart failure. These changes decreased dramatically after adrenalectomy. An interesting observation was marked increase in expression of atrogin-1 mRNA and protein compared to the idiopathic DCM and control groups, which reduced dramatically after adrenalectomy. Atrogin-1 is a L3 ligase enzyme expressed in skeletal, smooth, and cardiac muscle. It is overexpressed in sarcopenic muscle of aged individuals. Atrogin-1 functions in the ubiquitination of proteins, which is essential for directing intracellular proteins to proteasomes for degradation. This pathway could be a target for therapeutic intervention in severe cardiomyopathy of Cushing's syndrome where resolution of hypercortisolaemia is difficult, although this remains to be tested.

What is the clinical relevance of these cortisol specific changes in the heart and their impact on cardiovascular events and mortality in Cushing's syndrome? Several observations are pertinent here. First, there is no systematic large scale study of the frequency of the aforementioned changes. Second, there are no long-term (> 18 months) follow-up studies in patients with the described changes. Third, with successful treatment of hypercortisolaemia the changes are largely,...
although not always, completely reversible. Fourth, for patients, apart from those with the rare dilated cardiomyopathy, the functional consequences are not clearly described and are likely ‘subclinical’. Fifth, it is unclear whether these changes impact on cardiovascular events and mortality because there are no studies that have examined specific cardiac changes particularly in the mortality studies.

The conclusion is that, although interesting, these observations are likely relatively less important than atherosclerotic, blood pressure, and metabolic changes in determining mortality in Cushing's patients.

3 | Atherosclerosis

The structural changes in large/medium-sized blood vessels that have been shown to have a direct relationship with myocardial infarction, stroke, aneurysms, and other vascular events in the general population are well-known and include: diffuse increased thickness of the intima media layer of carotid and other large vessels (IMT); increased number of carotid and coronary artery plaques; increased arterial stiffness and reduced distensibility; increased calcification in coronary arteries; and reduced flow-mediated dilatation of the brachial artery.

These are all increased/decreased in patients with untreated Cushing's syndrome compared with age and body mass index (BMI)-matched controls. The pathogenesis of these changes is multifactorial and includes glucose intolerance/insulin resistance, abdominal obesity, dyslipidaemia, prothrombotic tendency, and probably chronic increases in inflammatory markers, as briefly reviewed by De Leo et al. This section examines to what extent changes in the vasculature are reversible after ‘cure’ of hypercortisolaemia.

The first systematic study, from Naples, of 15 patients examined 5 years after ‘cure’ found carotid artery IMT to be significantly increased, and lumen diameter, peak flow velocity, and distensibility coefficient all significantly reduced, compared to age and sex-matched controls. However, compared with BMI-matched controls these changes were less marked, highlighting the use of appropriately matched controls. Some although not all features of metabolic syndrome remained higher in patients vs. BMI matched controls, the most significant of which was waist-hip ratio (WHR). Interestingly, in this early study, neither fasting insulin, nor WHR predicted carotid IMT or distensibility coefficient. The study emphasises the crucial fact that the control group should be matched for WHR because this has subsequently been shown to be a more reliable than BMI as a determinant of features of metabolic syndrome. A subsequent study from the same group by Faggiano et al examined the carotid arteries of 25 Cushing's disease patients studied before and 1 year after cure compared to 32 age-, sex-, and BMI-matched controls. IMT was significantly increased and distensibility coefficient reduced vs. BMI-matched controls pre-treatment, and these variables improved after ‘cure’, although they remained higher than in the non-BMI-matched controls but were no different from BMI-matched controls. WHR was a significant determinant of IMT and distensibility coefficient both pre- and post-treatment. The only metabolic syndrome parameter that remained different from BMI-matched controls was 2 h post glucose insulin level. In the study, eight of 25 (32%) of patients vs. two of 32 (6%) of BMI-matched controls had carotid artery plaques and their diameters and IMT of their carotid arteries remained the same as before treatment, and so there was no improvement with ‘cure’.

Lupoli et al published a meta-analysis of 14 studies examining IMT, carotid plaque prevalence, and flow-mediated dilatation of the brachial artery (FMD). Of 10 studies evaluable, IMT was significantly higher in active Cushing's syndrome patients than in controls (but it is unclear whether the latter were all BMI or WHR matched). Post ‘cure’, three out of studies reported that the difference in IMT between patients and controls persisted but, in one (vide infra), IMT was no different in ‘cured’ patients vs. controls. Overall, there was no statistically significant difference in IMT between ‘cured’ patients and controls. The prevalence of carotid plaques was significantly higher in active Cushing's syndrome (five studies) and remained so post-‘cure’ (three studies). FMD was lower in active Cushing's syndrome than controls (three studies), and no post-‘cure’ studies were available at that time (but vide infra). In their meta-regression analysis Lupoli et al showed that, of the factors contributing to IMT, the mean difference in IMT between active Cushing's syndrome and controls was negatively correlated with age, obesity, and diabetes, and positively correlated with ACTH dependence, urinary cortisol, and serum cortisol. This shows that the older, more obese, and diabetic the patient with Cushing's syndrome, the lower the impact of Cushing's syndrome on IMT, suggesting that ‘general population’ risk factors may be as important in this context. Nevertheless, there is a suggestion that the degree of hypercortisolaemia may have a role to play in determination of IMT, although this requires further clarification. Lupoli et al state that, by only analysing studies that used BMI-matched controls (six out of 14) the meta-regression analysis results were confirmed but the data were not shown. Although this meta-analysis is interesting and contains the greatest number of active Cushing's syndrome patients for IMT analysis, there are far fewer patients in the ‘cured’ Cushing's syndrome group, and especially for carotid plaques and FMD analysis. Moreover, there is considerable heterogeneity between studies.

One study has examined FMD in a small number (n = 14) of Cushing's syndrome patients at least 4 years after ‘cure’ but, unfortunately, there is no pre-treatment data for comparison in the same patients. FMD and measures of arterial stiffness were no different in ‘cured’ patients and controls. IMT and number of carotid plaques were also no different in the ‘cured’ patients. It was stated that metabolic comorbidities at the time of study were ‘well controlled’ although 30% of patients were hypertensive, 20% had dyslipidaemia, and 7% had diabetes. Mean BMI was the same in both patients and controls but was only marginally in the overweight range and certainly not obese. The conclusion was that vascular health, at least 4 years after ‘cure’ of Cushing's syndrome, is similar to that of a healthy control population provided that co-morbidities are well-controlled and, moreover, the effects of previous hypercortisolaemia on the vasculature may be reversible. Although this latter suggestion may well be the case, it is certainly evident from the study and the meta-analysis of Lupoli et al that detailed attention to the comorbidities of is paramount importance.
What of the coronary arteries? A study by Neary et al.\textsuperscript{17} of 15 active Cushing's syndrome patients (14 of whom had ectopic Cushing's syndrome) revealed a greater number of both calcified and non-calcified coronary artery plaques in the Cushing's syndrome patients using multidetector computed tomography (MDCT). There were no post-treatment data in the study. However, a study by Barahona et al.\textsuperscript{18} using the same methods, in a sample of 29 patients ‘cured’ of Cushing’s syndrome for a mean of 11 years (very wide range), showed that there was a tendency to greater prevalence of coronary calcifications and non-calcified plaques in the patients than the controls. In the whole patient cohort, this was not statistically significant but, in women ($n = 24$), 42% had an abnormal MDCT vs. 18% for controls ($p \leq 0.05$), and, in 10 subjects (9 women) < 45 years old, 30% had non-calcified plaques vs. no plaques in controls ($p \leq 0.01$). Of the ‘cured’ women, 29% had hypertension vs. 6% of controls and they also had a significantly higher BMI than controls. Thus, as with carotid atherosclerosis, similar conclusions appear to apply to the coronary arteries: persistence of vascular disease despite ‘cure’ and persistence of two other major risk factors namely hypertension and obesity.

No review of atherosclerosis is complete without a brief mention of changes in metabolic risk factors for atherosclerosis after ‘cure’ of Cushing's syndrome. In the study from Naples conducted 5 years after ‘cure’,\textsuperscript{13} WHR, glucose stimulated glucose and insulin levels, and fibrinogen were all higher and high-density lipoprotein-cholesterol levels lower than in BMI-matched controls. Another study of 58 Cushing's syndrome patients after 5 years in remission revealed significantly higher waist circumference, WHR, and percentage of truncal fat as measured by dual-energy X-ray absorptionmetry scanning than BMI-matched controls.\textsuperscript{19} There was no difference in insulin resistance (Homeostatic Model Assessment for Insulin Resistance) and the only lipid abnormality was a higher triglyceride level,\textsuperscript{19} although 7% and 12% were diabetic and hypercholesterolaemic respectively, vs. 0% for controls.\textsuperscript{19} In the study by Barahona et al.,\textsuperscript{20} total and truncal fat mass was significantly greater 11 years after ‘cure’ than for BMI-matched controls. The aforementioned studies were all cross-sectional studies. Study of the same patients before and 1 year after ‘cure’ (longitudinal study) showed a reduction in the prevalence of impaired glucose tolerance and diabetes, although these measures were still greater than in BMI-matched controls.\textsuperscript{21} Waist circumference and dyslipidaemia were also higher 1 year post-‘cure’.\textsuperscript{21} In our own multicentre study,\textsuperscript{5} 10% of 320 patients 10 years after ‘cure’ were still taking antidiabetic medication, although we did not compare this with pre-treatment or with a control population. In a study from New Zealand, Bolland et al.\textsuperscript{22} report that, a mean of 6 years after presumed ‘cure’, the percentage of patients with diabetes (approximately 6%) was the same as at presentation, and so there was no improvement in this cohort in this parameter. These studies are representative of the literature on this topic with a consensus that, although improved, the adverse metabolic features of Cushing's syndrome do not normalise and so require constant monitoring/treatment to reduce cardiovascular risk as much as possible.

4 | HYPERTENSION

Systolic and diastolic hypertension is prevalent (up to 80%) in active Cushing's syndrome and is caused by multiple factors, as reviewed by Barbot et al.\textsuperscript{23} How is this affected by ‘cure’? Barbot et al.\textsuperscript{23} state that hypertension persists in approximately 30% of ‘cured’ patients. In the study by Faggiano et al.,\textsuperscript{14} 1 year after ‘cure’, both systolic and diastolic blood pressure (BP) were similar to that of BMI-matched controls and reduced compared to pre-treatment. In the study by Giordano et al.,\textsuperscript{21} the prevalence of hypertension, although reduced, was still much higher than in controls 1 year after ‘cure’, at between 40%–50% of patients. After surgical ‘cure’ of Cushing's syndrome, 80% of patients achieved remission or improvement in hypertension within 10 days of surgery, although, at 1 year, 27/42 (64%) patients had normal BP.\textsuperscript{24} Follow-up data were not available for 33/75 (44%) and so it is unclear what the real proportion is who achieved normotension at 1 year.\textsuperscript{24} In the study by Wagenmakers et al.\textsuperscript{19} 31% of 58 patients 5 years after ‘cure’ were still hypertensive. In our own study,\textsuperscript{7} 10 years after ‘cure’, 50% of 320 patients were being treated for hypertension. In the New Zealand series,\textsuperscript{22} the prevalence of hypertension was still 50% 6 years after ‘cure’, down from 74% at the time of diagnosis, showing an improvement but certainly still being prevalent. As with atherosclerosis risk markers, although hypertension is improved and, in some studies, the number and dose of antihypertensive medications can be reduced, there is persistence of hypertension requiring systematic and constant review.

5 | RELATIONSHIP BETWEEN CARDIOVASCULAR COMPLICATIONS, CARDIOVASCULAR MORBIDITY, AND MORTALITY IN CUSHING’S SYNDROME

It is well documented in several reports that mortality from cardiovascular causes is still above that of the general population in ‘cured’ Cushing's syndrome patients. There is no systematic review or meta-analysis of any relationship between cardiovascular risk factors and a reduction or otherwise in non-fatal cardiovascular events specifically in these patients. However, the New Zealand study\textsuperscript{22} shows a significant doubling of patients with non-fatal ischaemic heart disease and tripling of non-fatal cerebrovascular disease a mean of 6 years after a presumed ‘cure’. Accordingly, the prevalence of these comorbidities progressed despite continued normalisation of hypercortisolism. The explanation is likely the persistence of the risk factors discussed earlier, although further ageing might also contribute. There are two studies that have looked at hazard ratios (HR)\textsuperscript{25} and standardised incidence ratios (SIR)\textsuperscript{26} of cardiovascular events in long-term follow-up of treated Cushing's syndrome patients. Dekkers et al.\textsuperscript{25} reported a fully adjusted (including age,sex, hypertension, diabetes) HR of 2.8 (1.8–4.4 95% confidence interval) for acute myocardial infarction; 0.8 (0.3–1.7) for heart failure; and 1.5 (0.9–2.5) for stroke 1–30 years after diagnosis and treatment. Significance values are not reported but, because the confidence interval for heart failure and stroke overlap, these are
TABLE 2

| Number of patients | Hypertension | Diabetes |
|--------------------|--------------|----------|
|                    | HR (95% CI)  | Significance (p) | HR (95% CI)  | Significance (p) |
| Bolland et al 22   | 253          | 3.2 (1.4–7.4)    | < 0.001 | 3.6 (1.2–10.4) | < 0.02 |
| Lambert et al 30    | 346          | 3.3 (0.998–10.9) | 0.051 | 2.64 (1.5–5.0) | 0.0009 |
| Clayton et al 31a   | 320          | 1.59 (0.77–3.31) | 0.08 | 2.86 (1.29–6.2) | 0.009 |
| Ragnarsson et al 31 | 502          | 0.8 (0.5–1.2)    | 0.28 | 1.2 (0.07–2.2) | 0.5 |

Notes: Of four other studies (Dekkers et al, 25 Hassan-Smith et al, 32 Ntai et al, 28 and Yaneva et al, 29), there is no independent analysis for hypertension or diabetes.

Hazard ratios (HR) by Cox’s multivariate regression analysis do not contain all the same variables and depend on models used in the studies.

Multicentre (six) study. 5Patients with pituitary Cushing’s disease only.
Abbreviation: CI, confidence interval.

6 | DEPRESSION AND MORTALITY IN CUSHING’S DISEASE

It is well known that there are significant long-term changes in the brain with cortisol excess (reviewed by A Periera). Depression is very common in Cushing’s syndrome pre-treatment and persists after ‘cure’ in a proportion of patients. In the non-Cushing’s population, depression is a risk factor for myocardial infarction, although the extent to which depression is a factor in cardiovascular mortality in Cushing’s syndrome has not been systematically assessed. However, in the study by Lambert et al, 30 depression pre-treatment was a significant risk factor in one model of overall mortality. The study did not analyse cardiovascular mortality separately. Suicide was reported to be associated with increased mortality in a recent study between 1 and 28 years after diagnosis. However, there were only six deaths from suicide, three of whom were in remission at the time and one was not. The remission status was not known in two patients. Although these data are interesting, further study is needed before concluding that depression and suicide significantly impacts cardiovascular morbidity and mortality in Cushings disease in the long-term in ‘cured’ patients.
7 | OVERALL CONCLUSIONS

Insofar as the evidence comes from large individual studies, it is reasonable to conclude that diabetes and hypertension are likely independent risk factors for long-term cardiovascular morbidity and mortality in Cushing's syndrome. This conclusion has the caveat of requirement for verification from large definitive longitudinal studies with sufficient numbers of events for meaningful statistical analysis. As regards dyslipidaemia and cardiac disease, there are no substantive data. Notwithstanding this, it remains important to treat all these comorbidities aggressively as one would for the general population. In this regard, treatment should be supervised by experts with in-depth knowledge of Cushing's syndrome and, if not undertaking this personally, at least in close collaboration with generalist physicians. It needs to be emphasised to healthcare funders/providers that the care of Cushing's syndrome patients is a lifelong undertaking. It is not sufficient to just restore eucortisolaemia and ensure that this is maintained lifelong. It is also important to remember that, although uncommon, Cushing's syndrome is a chronic disease requiring continued monitoring by an expert team.

This article is part of an update series on the diagnosis and treatment of Cushing's syndrome.36–52

AUTHOR CONTRIBUTIONS

richard clayton: Conceptualization; data curation; formal analysis; funding acquisition; investigation; methodology; project administration; writing – original draft; writing – review and editing.

CONFLICTS OF INTEREST

The author declare that they have no conflicts of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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