Growth Hormone and Cardiovascular Risk Factors

Journal of Clinical Endocrinology and Metabolism
Volume 90 • Number 3 • March 2005

CLINICAL REVIEW: Growth Hormone and Cardiovascular Risk Factors

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Received March 21, 2004.
Accepted November 29, 2004.

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[F]Abbreviations:

apo
: Apolipoprotein

GHD
: GH deficiency or deficient

HDL
: high-density lipoprotein

IDL
: intermediate-density lipoprotein

LDL
: low-density lipoprotein

Lp(a)
: lipoprotein (a)

LV
: left ventricular

NO
: nitric oxide

PAI
: plasminogen activator inhibitor

VLDL
: very low-density lipoprotein

The aim of this article is to review the lessons on the relationship between GH and the principal metabolic cardiovascular risk factors that we learned from studies of GH deficiency (GHD) in the adult. The lesson that "organic" GHD has taught us is that primary impairment in the GH/IGF-I axis may lead to a high-risk cardiovascular profile that is partially reversible during GH replacement. Waiting for the definitive demonstration that GH substitution may reduce cardiovascular mortality in these patients, we find that data so far reported are encouraging and indicate in the beneficial cardiovascular effects of GH one of the major factors supporting this type of treatment in hypopituitary GHD adults. Moreover, enough evidence from GHD studies has been produced to suggest a physiological role for the GH/IGF-I axis in the control and regulation of several metabolic cardiovascular risk factors. (*J Clin Endocrinol Metab* 90: 1864–1870, 2005)

GH DEFICIENCY (GHD) has only recently been recognized as a clinically relevant condition in adults [1] . Among the distinct features of the GHD syndrome, the cardiovascular involvement has convincingly emerged as particularly important [2] . Studies in this field also allowed a physiological role for GH in the regulation of heart function and structure to be elucidated or at least envisaged [3] .

The aim of this perspective article is to review the lessons that we learned from the study of GHD about the relationship between GH and the main metabolic cardiovascular risk factors. This can be helpful for evaluating the potential involvement of "subclinical" or "functional" GHD, which is observed for example in aging and obesity, in the increase of cardiovascular risk.

Cardiovascular Mortality

Recent epidemiological studies have shown that hypopituitarism in adults may be associated with increased cardiovascular death [4] . Rosen and Bengtsson were the first to demonstrate that life expectancy in hypopituitaric patients untreated for GHD was decreased [5] . The excess mortality reflected deaths from vascular disease. Myocardial infarction, ischemic heart disease with congestive cardiac failure, and cerebrovascular disease were the most frequent causes of vascular death. In fact, in a retrospective study in 333 Swedish patients, standardized mortality risk was found to be almost doubled and

was primarily the result of excess deaths from vascular disease (58% of total number of deaths), such as ischemic heart disease and cerebrovascular disease [5] . These findings were confirmed in the United Kingdom and in Sweden [4] [6] . In the latter study, the increased vascular risk was mostly attributable to cerebrovascular disease and was more prevalent in women than in men [6] . More recently, excess mortality was confirmed in a large prospective trial involving 1014 hypopituitaric patients in the United Kingdom. Excess mortality resulted from cardiovascular causes. In this study, the influence of GHD on mortality rate cannot be assessed, because GH reserve was only measured in a small number of patients [2] . Interestingly, isolated GHD has also been reported to be associated with increased mortality [7] . Finally, GH **replacement** has recently been suggested to provide protection from fatal myocardial infarctions in hypopituitary adults [8] .

Vascular Atherosclerosis

Endothelial dysfunction is an early step in the atherogenic process [9] . Atherogenesis begins long before the presence of clinically detectable disease with the deposition of lipids in the intima of systemic arteries to form fatty streaks [10] . Endothelial dysfunction is a potentially reversible event in the pathogenesis of atherosclerosis and predisposes to thrombosis, leukocyte adhesion, and smooth muscle proliferation within the arterial wall [11] . Impairment of flow-mediated brachial artery dilatation has been demonstrated with all known risk factors for atheroma, including high serum cholesterol, high blood pressure, insulin-dependent and noninsulin-dependent diabetes mellitus, as well as active smoking and hyperhomocysteinemia [12] . Therefore, classic and nontraditional risk factors have been shown to be associated with endothelial dysfunction leading to impairment of nitric oxide (NO) release, increased oxidative stress, and loss of protection against the atherogenic process [13] .

Recent evidence has demonstrated that insulin resistance in the absence of overt type 2 diabetes or the metabolic syndrome results in endothelial dysfunction in peripheral and coronary vasculature. Evidence also indicates that endothelial dysfunction itself could contribute to insulin resistance. Thus, treatment strategies that attenuate cardiovascular disease may also attenuate insulin resistance progression [14] . Elucidating the common mechanisms that mediate these events will be important in understanding their intimate relation.

Hypopituitary GHD adults have been shown to have an increased number of atheromatous plaques in carotid and femoral arteries, compared with control individuals. Evidence for a tendency for increased atheromatosis in GHD patients comes from studies with arterial ultrasonography [15] . Other markers of atheromatosis found in GHD patients include a greater intima-media thickness, more stiffness of carotid arteries, and less aortic distensibility [16] . These findings have been reported in both young adults [17] and elderly subjects [18] with GHD and in childhood-onset [17] and adulthood-onset GHD [18] . Intima media thickening represents the earliest morphological change in the arterial wall in the

process of atherogenesis and is an independent predictor of acute myocardial infarction in men [10] .

In a double-blind placebo-controlled study, one recent important finding was that GHD is associated with decreased systemic NO formation [19] . Baseline urinary nitrate and cGMP excretion rates, a mirror of systemic NO synthesis rates, were found substantially lower in the GHD patients than in age- and sex-matched controls. Indeed, these indices of NO formation were as low in patients with GHD as in patients with peripheral arterial occlusive disease and generalized atherosclerosis, whereas those in the control group were comparable with the values found in young healthy volunteers.

The cause of impaired NO activity in atherosclerotic patients remains unclear. There may be a more evident reason for impaired NO activity in GHD patients, because GH exerts at least part of its effects via IGF-I, and IGF-I has been shown to have a direct stimulatory effect on NO synthesis [20] . In fact, endothelial cells possess receptors for IGF-I and IGF-I is able to increase NO production *in vitro*, thus contributing to the modulation of vascular tone. A reduction of IGF-I production is associated with a reduction of arterial vasodilatation and increased platelet aggregability. During human GH replacement therapy, urinary nitrate excretion reached values that were comparable to healthy age-matched controls [19] . Because IGF-I is not invariably decreased in GHD [21] , the observed effects on NO may also be, at least in part, directly due to GH itself as has been previously shown in coronary arteries [22] . The effect on intima-media thickness of long-term GH replacement in hypopituitaric patients has been investigated in an open study that has shown a potent inhibitory effect of 1-yr GH replacement on intima-media thickness progression, which was maintained after 2 yr, indicating that this effect of GH may not be transient [23] . In addition, Pfeifer *et al.* [24] demonstrated in an open study that the decreased response of brachial artery blood flow hyperemia in GHD compared with control men was also reversed after 18 months of GH treatment. Taken together, these results indicate that in GHD adults the vasodilatory function of the endothelium is impaired and it improves with GH treatment.

Inflammatory Cardiovascular Markers

Homocysteine

Abnormal homocysteine metabolism is a potential link between GHD and the observed increase in vascular mortality because an elevated plasma homocysteine concentration has been identified recently as an independent risk factor for atherosclerosis [25] . Hyperhomocysteinemia is linked to oxidative stress, endothelial dysfunction, and genesis of atherothrombotic vascular disease. The plasma level of homocysteine is affected by several factors. Plasma homocysteine levels increase with age, in renal impairment, in folate and vitamin B12 deficiency, and in hypothyroidism. Some studies report higher plasma homocysteine levels in postmenopausal than premenopausal women [26] . Conflicting results have been reported on plasma homocysteine levels in GHD adults

compared with matched controls, showing either increased or normal homocysteine in organic GHD [27] [28] . A recent randomized controlled trial indicated that the levels of homocysteine in GHD patients were high at baseline, in a range associated with high cardiovascular risk [29] . With GH treatment, homocysteine levels decreased by nearly 8%. The clinical significance of the magnitude of this decrement is not yet certain. Interestingly, the results are similar to those recently reported for hormone replacement therapy with estrogens and raloxifene when administered to healthy postmenopausal women [30] .

C-reactive protein

C-reactive protein is a useful prognostic tool in the evaluation of cardiovascular risk. Prospective studies have consistently shown a relation between C-reactive protein levels and risk for cardiovascular events [31] . The mean C-reactive protein level in men with organic GHD in a recent randomized single-blind placebo-controlled study at baseline was in the highest quartile referred to values in the Physicians' Health Study (3-fold increased risk for future myocardial infarction and 2-fold increased risk for stroke, independent of other cardiovascular risk factors) [32] . C-reactive protein levels declined in half of the GH-treated men by one (37.5%) or two (12.5%) quartiles, as defined by the Physicians' Health Study. Approximately one third of patients (31%) experienced reductions without changes in quartiles, and slight increases occurred in a few patients (19%). To date, few therapies have been shown to influence serum C-reactive protein levels [33] . Of interest, the absolute mean reduction compared with placebo in this randomized study with GH [32] is similar to the reduction reported for pravastatin in patients from the CARE study [33] .

Fibrinogen and plasminogen activator inhibitor (PAI-1)

Abnormalities in coagulation factors suggestive of a defective fibrinolytic system, elevated tissue PAI, fibrinogen, and factor VII, have been reported in GHD adults [34] . Colao *et al.* [35] in a recent prospective open study demonstrated that both treated and untreated GHD adults had elevated fibrinogen levels when compared with healthy subjects, and in a cohort of younger adult patients with either childhood-onset or adult-onset GHD, 12 months of GH replacement significantly reduced fibrinogen levels. Fibrinogen concentrations, however, remained abnormal compared with age-and sex-matched controls [35] . In another open study on 17 patients with adult-onset GHD during 2 yr of GH treatment, PAI-1 activity, PAI-1 antigen, and antigen tissue plasminogen activator decreased during long-term treatment [36] . These changes may be a direct effect of GH itself or may be secondary to the favorable changes in body composition. It remains to be seen whether changes in these fibrinolytic variables during recombinant human GH treatment may reduce the cardiovascular risk in patients with GHD.

Cardiac Morphology

In young adults with GHD, the impairment of cardiac performance presents as reduction in left ventricular (LV) mass, decreased ejection fraction, and abnormal LV diastolic filling. Some studies have demonstrated a decrease in the thickness of the LV posterior wall and of intraventricular septum in patients with GHD. A significant decrease of 14% of the LV ejection fraction was also observed [37] . Other studies reported a decrease in LV posterior wall without any difference in LV internal diameter and systolic function evaluated as ejection fraction between GHD patients and controls. In an open study, Cuocolo *et al.* [38] evaluated cardiac function in 14 adults with GHD and 12 matched controls using radionuclide scanning. Compared with controls, the patients had decreased LV ejection fraction, decreased stroke volume index, and decreased cardiac index. GH therapy for 6 months reversed these deficits in cardiac function. In fact, 6 months of GH replacement have been showed to increase LV mass (18%), stroke volume (28%), and cardiac output (43%) and to reduce peripheral vascular resistance in GHD adults. However, 6 months after cessation of therapy, cardiac function had returned to baseline [38] . This is consistent with findings in patients with heart failure after acute GH infusion [39] .

IGF-I augments myocardial contractility by sensitizing myofilaments to Ca^{2+} [40] . IGF-I also retards cardiomyocyte apoptosis. These findings suggest that GH administration may have a marked trophic effect on the heart, particularly in patients with GHD. The effect of GH dose on the cardiac response in GHD has not been investigated so far. A relation between response of some cardiac parameters and amplitude of IGF-I response to GH treatment seems likely. This may also indicate that a better cardiac response is obtained in patients with more severe GHD as assessed by lower basal IGF-I levels [41] .

Finally, Maison and Chanson [42] in a metaanalysis of randomized and controlled clinical trials of GH treatment in adults with GHD, confirmed that GH treatment is associated with a significant positive effect on LV mass, intraventricular septum, LV end diastolic diameters and stroke volume, as assessed by echocardiography. In contrast, GH treatment was not found to have a significant impact on systolic parameters [42] .

Lipid Metabolism

Many epidemiological studies have demonstrated that elevated low-density lipoprotein (LDL) cholesterol level, low high-density lipoprotein (HDL) cholesterol level, and excess abdominal fat are associated with an increased risk of cardiovascular morbidity and mortality. Plasma lipid concentrations are dependent on the secretion and clearance rate of the apolipoprotein (apo) B containing lipoproteins [very low-density lipoprotein (VLDL) and intermediate-density lipoprotein (IDL)]. Because VLDL apo B is the precursor of IDL and LDL apo B, lipid kinetics are dependent on VLDL apo B metabolism. Hepatic overproduction of VLDL apo B has been implicated in a number of hyperlipidemic disorders known to be related to premature atherosclerosis [11] . Patients with GHD were associated with increased abdominal fat and compared with control individuals and were found to have elevated levels of total and LDL cholesterol in most studies [43] [44] . At the same time, in some but not all studies, serum triglycerides were

higher and HDL cholesterol levels were lower than expected in patients with GHD [45] . Abdu *et al.* [46] in a cross-sectional observational study have compared the lipid profile and coronary risk predicted by the Framingham heart study equation in GHD patients and age-and gender-matched controls. The conclusion of this work is that the changes of lipid profile may help to explain the increased coronary risk in GHD hypopituitary patients, particularly females. In both genders, there was an increase in the total to HDL cholesterol ratio, total LDL were increased in both sexes, and HDL and apo-1 were lower. There were no differences in apo B and lipoprotein (a) [Lp(a)] between patients and controls. The modification in the lipid profile is partly explained by an enhanced hepatic secretion and reduced catabolism of VLDL apo B, suggesting that the hyperlipidemic condition of these patients and consequently the increased risk for atherosclerosis may be in part related to a disordered VLDL apo B metabolism [47] .

Low IGF-I in GHD may be the primary mechanism underlying the abnormal body composition and central fat distribution and may also contribute to the hypercholesterolemia. In fact, adults with GHD have been shown consistently to have reduced skeletal muscle, reduced lean body mass, and increased fat mass. The distribution of this excess fat mass has been the focus of several studies, and these have demonstrated that fat accumulates in a central distribution, mostly in visceral tissue. In a randomized controlled trial, Salomon *et al.* [43] were the first to demonstrate that fat mass was higher by a mean of 7% in GHD patients compared with predicted value based on age, sex, and height. In epidemiological studies, this abdominal distribution has been associated with an increased risk of mortality and morbidity from cardiovascular disease [48] . GH receptor blockade through the administration of pegvisomant creates a state of acute GHD. Pegvisomant alone increased the serum triglyceride concentration, indicating that GH is directly involved in the regulation of serum triglycerides [49] . However, in a cross-sectional study in an elderly population, a strong negative correlation between free IGF-I and triglycerides was observed [50] . Moreover, administration of recombinant IGF-I has been reported to cause a decrease in triglyceride levels [51] . Taken together, these data indicate that GH and IGF-I are both involved in triglyceride metabolism. Several researchers in controlled clinical trials have reported that GH increases and IGF-I decreases circulating Lp(a) [44] [52] . Surprisingly, pegvisomant induced no change in Lp(a) [49] , suggesting that GH and IGF-I are, at least in the short-term, of only minor importance in the regulation of Lp(a).

Total and LDL cholesterol levels decrease significantly during short-term GH replacement therapy, but these initial effects have been reported to be lost during long-term therapy in some, even if not in all studies [43] [53] . Likely mechanisms of the effect of GH include both an increased expression of LDL receptors and an increased clearance of VLDL apo B lipoproteins [54] . Previous short-term open studies have demonstrated an effect of GH to decrease central body fat [55] [56] and decrease total cholesterol, with an increase in HDL cholesterol in some studies [53] [57] . Prolonged open studies suggested that GH therapy [58] had no significant effect on body weight, but it prevented the increase in waist circumference and waist-to-hip ratio that occurred in the patients without GH substitution. By bioimpedance analysis, GH therapy caused an increase in total body water and decrease in the percentage of body fat [58] .

Glucose Metabolism

Type 2 diabetes markedly increases the incidence of cardiovascular diseases. Numerous studies have shown that before the onset of diabetes subjects also have an adverse pattern of dyslipidemia and increased blood pressure. More recently, increased levels of inflammatory markers have been shown to be present in the prediabetic state. Insulin resistance is also related to increased inflammation. The progression of insulin resistance and its associated metabolic syndrome to diabetes parallels the progression of endothelial dysfunction to atherosclerosis, the major cause of mortality in individuals with diabetes [59] . As obesity is increasing in epidemic proportions in the United States and worldwide, so is the metabolic syndrome consisting of increased abdominal adiposity, elevated triglycerides, low HDL cholesterol, elevated blood pressure, elevated uric acid, high LDL cholesterol and albuminuria. Increasing evidence suggests that endothelial cell dysfunction, among the earliest recognized alterations in atherosclerosis, is present in insulin resistance. Although endothelial cell dysfunction occurs with individual components of the insulin resistance syndrome, it also occurs with only modest alterations in these risk factors in the presence of insulin resistance. The presence of endothelial cell dysfunction with a decrease in NO activity not only represents altered vasodilatory capacity but also strongly implies increased inflammation, oxidation, and thrombosis in the vascular wall. With the progression of insulin resistance, the incidence of coronary artery disease mortality also increases. Clearly, the progression of insulin resistance appears to parallel the progression of cardiovascular disease [60] .

Adults with GHD have altered body composition and tend to be obese, with an increase in central adiposity [61] [62] . A randomized controlled study of 24 adults with GHD demonstrated fasting insulin levels above the normal reference range and a significant positive correlation between fasting plasma insulin and both fat mass and waist girth [43] . Adults with GHD are thus likely to be insulin resistant. This has been confirmed in a hyper-insulinemic euglycemic clamp study of nine adults with GHD [63] . Similarly, using a hyperinsulinemic euglycemic clamp, Johansson *et al.* [64] demonstrated in a prospective study a decreased glucose infusion requirement in 15 adults with GHD compared with that in matched controls, indicating reduced insulin sensitivity. In a double-blind, placebo-controlled, cross-over study, Fowelin *et al.* [65] assessed the effects of 6 months of GH replacement on glucose metabolism in nine adults with GHD. After 6 wk of GH therapy, fasting glucose levels and plasma insulin concentrations were elevated, but both had returned to baseline at 26 wk. The amount of glucose required for euglycemia during the insulin clamp was significantly lower after 6 wk of therapy, but there was no difference above baseline at 26 wk. These changes were interpreted as a short-term reduction of insulin-stimulated glucose utilization, mediated by GH, with reversal of these changes with time, perhaps as a result of the GH-mediated change in body composition.

In summary, GHD adults have hyperinsulinemia, indicating insulin resistance. These features are associated with central obesity and increased intraabdominal adiposity. Most

of the hyperinsulinemic euglycemic clamp studies have confirmed this insulin resistance. In addition, there is evidence that adults with GHD have reduced hepatic glycogen stores. GH replacement has been demonstrated to further increase insulin resistance over a period of 1–6 wk of therapy, but carbohydrate metabolism returns to baseline after 3 months of GH treatment [66] . The long-term effect of GH substitution on insulin sensitivity in GHD adults is still controversial. However, in an open-label treatment trial, Svensson *et al.* [67] studied the effect of 7 yr of GH-replacement therapy on insulin sensitivity using the hyperinsulinemic euglycemic clamp technique in a small group of GHD patients. Blood glucose concentrations were transiently increased during the first year of treatment. There was a tendency for insulin sensitivity in the GHD patients, as compared with that in the controls, to be higher at study end than at baseline. This could suggest that GH-replacement therapy may prevent the age-related decline in insulin sensitivity in GHD. On the other hand, two patients developed type 2 diabetes mellitus during the study.

Finally, a systematic review of blinded, randomized, placebo-controlled trials of GH treatment in adult patients with GHD was recently published. Thirty-seven trials were identified. GH treatment significantly reduced LDL cholesterol, total cholesterol, and fat mass, and significantly increased lean body mass, fasting plasma glucose, and insulin. All effect sizes remained significant in trials with low doses and long duration [68] .

In conclusion, GHD appears to contribute to impaired glucose tolerance, hyperinsulinemia, and hypertriglyceridemia indirectly via the abnormal body fat distribution. With long-term GH administration, the cardiovascular risk will reflect the balance between its different actions. The antiinsulin effect of GH may be opposed by the beneficial effect for glucose homeostasis of the increase in muscle bulk and decrease in total and central adipose tissue mass. From available data, it is not yet clear which mode of action will prevail, because the effects on carbohydrate tolerance and insulin sensitivity tended to recover in some of the trials but not in others [69] [70] [71] .

Effect of Age of Onset and Gender on Cardiovascular Risk

Childhood- vs. adult-onset GHD

Adult GHD is not a totally homogeneous clinical condition. The clinical presentation may differ depending on the underlying pituitary disease, the severity of GHD and the presence of other anterior hormonal deficiencies [72] [73] . Furthermore, the clinical presentation may differ whether the pituitary disease was acquired in childhood or in adult life. In a randomized controlled study by Attanasio *et al.* [74] , patients with childhood-onset GHD had lower serum IGF-I level, lower body mass index, higher serum HDL cholesterol level, and better quality of life than patients with adult-onset GHD. In a study in which these two groups were closely matched for age, height, and weight, both groups had a similar degree of LV systolic dysfunction [75] . Little is known about differences in responsiveness to GH treatment between these two groups of patients.

In a single-center, prospective open study, baseline differences in 21 consecutive adults with childhood-onset GHD and 21 closely matched adults with adult-onset GHD were compared. Furthermore, the effects of 5 yr of GH replacement therapy on body composition and metabolic parameters in these patients were investigated. This study revealed marked differences in the baseline characteristics of the patients. Childhood-onset patients were shorter, had increased body fat (observed/predicted ratio), decreased serum IGF-I concentration, and lean body mass. Serum cholesterol was higher in patients with adult-onset GHD. The treatment responses were more marked in the childhood-onset patients in terms of lean body mass, whereas a reduction in serum cholesterol concentration was observed only in the adult-onset patients. After 5 yr of GH therapy, no differences remained between the two study groups after correction for body height [76] .

Sex-related differences

It has been observed that the risk factor profile was worse in GHD women compared with their sex-matched controls than in GHD men compared with their controls. Also, previous results indicated that the increased mortality previously observed among GHD women [28] may be due to a more negative risk factor profile including increased body mass index in GHD women. When analyzed by gender, the beneficial effect of GH seemed greater in men *vs.* women for the increment in IGF-I, increase in lean body mass, and increase in total body water [77] . In a recent double-blind, randomized, placebo-controlled study, IGF-I levels in men increased into the supraphysiological range using a GH dosing scheme, which consisted in a fixed, weight-based dose that could be modified only when side effects occurred [78] . Despite receiving the same average dose of GH, women had IGF-I responses that led to normal age-adjusted IGF-I levels. Perhaps as a consequence of the differences in IGF-I responses, the decrease in fat mass was greater in men than in women, and the salutary changes in LDL cholesterol were more evident in men than in women. These findings indicate that premenopausal women are somewhat resistant to the effects of GH. In fact, sex steroids and in particular estrogens may influence the ability of GH to stimulate IGF-I as well as GH production rate [79] . Finally, in a randomized double-blind controlled study, Ezzat *et al.* [80] showed that interestingly GH replacement therapy in adults with GHD demonstrated beneficial effects on lean body mass evaluated by dual energy x-ray absorptiometry that were more pronounced in males than females. In contrast, cardiac function improvement evaluated by echocardiography appeared to benefit both genders equally, suggesting different tissue sensitivity to GH/IGF-I according to the sex hormone milieu [80] .

Conclusions

The lesson that "organic" GHD has taught us is that primary impairment in the GH/IGF-I axis may lead to a high-risk cardiovascular profile (increased body fat, insulin resistance, hypertriglyceridemia) that is partially reversible during GH replacement.

Waiting for the definitive demonstration that GH substitution may reduce cardiovascular mortality in these patients, data so far reported are encouraging and indicate in the beneficial cardiovascular effects of GH one of the major factors supporting this type of treatment in hypopituitary GHD adults. Moreover, enough evidence from GHD studies has been produced to suggest a physiological role for the GH/IGF-I axis in the control and regulation of several metabolic cardiovascular risk factors. Therefore, it is intriguing to speculate that the clinical implications of these findings may be extended from situations of organic GHD to conditions such as aging and obesity characterized by "functional" GHD. However, long-term large clinical studies are needed to support this interesting hypothesis.

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