Role of insulin resistance in kidney dysfunction: insights into the mechanism and epidemiological evidence

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Abstract
Several lines of evidence suggest a pathogenic role of insulin resistance on kidney dysfunction. Potential mechanisms are mostly due to the effect of single abnormalities related to insulin resistance and clustering into the metabolic syndrome. Hyperinsulinemia, which is inevitably associated to insulin resistance in non diabetic states, also appears to play a role on kidney function by inducing glomerular hyperfiltration and increased vascular permeability. More recently, adipocytokine which are linked to insulin resistance, low grade inflammation, endothelial dysfunction and vascular damage have been proposed as additional molecules able to modulate kidney function. In addition, recent evidences point also to a role of insulin resistance at the level of the podocyte, an important player in early phases of diabetic kidney damage, thus suggesting a new mechanism through which a reduction of insulin action can affect kidney function. In fact, mouse models not expressing the podocyte insulin receptor develop podocyte apoptosis, effacement of its foot processes along with thickening of the glomerular basement membrane, increased glomerulosclerosis and albuminuria.

A great number of epidemiological studies have repeatedly reported the association between insulin resistance and kidney dysfunction in both non diabetic and diabetic subjects. Among these, studies addressing the impact of insulin resistance genes on kidney dysfunction have played the important role to help establish a cause-effect relationship between these two traits.

Finally, numerous independent intervention studies have shown that a favourable modulation of insulin resistance has a positive effect also on urinary albumin and total protein excretion.

In conclusion, several data of different nature consistently support the role of insulin resistance and related abnormalities on kidney dysfunction. Intervention trials designed to investigate whether treating insulin resistance ameliorates also hard renal end-points are both timely and needed.

Keywords: diabetic kidney disease; genetic susceptibility; insulin sensitizers; insulin signalling; metabolic syndrome

Introduction
Kidney dysfunction is a major cause of morbidity and mortality whose prevalence, mainly because of population ageing, is rising worldwide [1]. Also the epidemics of abnormalities clustering with insulin resistance [2] might have played a role in increasing the prevalence of kidney dysfunction [3].

This review article will address such relationships, particularly among diabetic patients. First, potential mechanisms linking insulin resistance to kidney dysfunction will be discussed. Then, epidemiological data on the relationship between these two abnormalities will be reported. In this context, data on the association between variability of ‘insulin resistance genes’ and kidney function will be offered to better address the nature of such relationships. Finally, data from intervention studies reporting amelioration of kidney dysfunction obtained by insulin-sensitizing treatment will be summarized. These latter data not only reinforce the hypothesis that insulin resistance causes kidney dysfunction, but also point to a potential new tool for preventing worsening of kidney function and/or providing a better treatment of kidney dysfunction.

Mechanisms linking insulin resistance to kidney dysfunction

(i) Abnormalities related to insulin resistance
Some of the general mechanisms linking insulin resistance-related abnormalities to kidney dysfunction are shown in Figure 1. We assume here the most simple scenario which is that insulin resistance affects in a similar
fashion and degree all organs of a given individual. Whether this is true for all individuals or whether, in some cases, insulin resistance specifically affects only a subset of tissues or organs is an exciting question which deserves much attention and effort to find an answer. Each single component of the constellation of abnormalities clustering under the definition of metabolic syndrome (MetS), including abnormal blood pressure, atherogenic dyslipidaemia, excess of adiposity and abnormal glucose homeostasis, may in fact play a role in kidney damage. The mechanisms of hypertensive injury leading to chronic kidney disease (CKD) are mainly due to intraglomerular hypertension [4]. Obesity causes focal segmental glomerulosclerosis and glomerulomegaly mostly through hemodynamic changes and the overproduction of several adipocytokines and growth factors [4]. Several lines of evidence suggest that atherogenic dyslipidaemia, characterized by low-density lipoprotein, initiates endothelial damage and eventually induces renal dysfunction [4]. Finally, hyperglycaemia causes kidney damage through the activation of complex pathways including exacerbated polyol and hexosamine flux, increased formation of advanced glycation end-products (AGE), activation of protein kinase C (PKC) isoforms and, eventually, low-grade chronic inflammation [4]. A critical role in hyperglycaemia-induced kidney damage is also played by transforming growth factor (TGF)-β whose profibrotic activity leads to increased production of extracellular matrix by mesangial cells [4]. Hyperinsulinaemia, which is inevitably associated to systemic insulin resistance in non-diabetic states, also plays a role by inducing glomerular hyperfiltration, endothelial dysfunction and increased vascular permeability [5], all converging to albuminuria. Furthermore, through exaggerated stimulation of sympathetic nervous system activity and renal sodium reabsorption, hyperinsulinaemia increases glomerular capillary pressure and protein traffic, thus further contributing to renal damage. In addition, impaired insulin sensitivity is associated with altered renal cellular metabolism and electrolyte composition, mesangial hyperplasia, renal hypertrophy, increased endothelial

**Fig. 1.** Pathogenic mechanisms linking insulin resistance to kidney dysfunction. The constellation of abnormalities related to insulin resistance including those clustering in the metabolic syndrome, adipocytokine dysregulation, hyperinsulinaemia and low-grade inflammation are all involved in worsening kidney function. Several biochemical and molecular pathways are involved in mediating the effect of the above described abnormalities on kidney function. Dysregulation of polyol and hexosamine fluxes, AGE, activation of PKC isoforms are mostly a consequence of hyperglycaemia. Abnormalities in the insulin-signalling pathway, possibly, but not exclusively, due to adipocytokine-induced activation of JNK, IKK and specific PKC isoforms and/or to imbalance between the PI3K/Akt (which is impaired) and MAPK (which is exacerbated) axes also play a role by reducing NO-dependent vasodilation and increasing vasoactivity and angiogenesis, well-established promoters of kidney dysfunction. Profibrotic elements and vascular growth factors, among which TGF-β is the most well studied, are also involved in damaging glomerulus function through overproduction of mesangial cell matrix and thickening of the glomerular basement membrane which eventually end in albumin leakage. Finally, an emerging role of podocyte-specific insulin resistance is recently proposed with podocyte function, structure and survival being heavily affected by abnormal insulin signalling, thus further contributing to reduced kidney function. Abbreviations: AGE, advanced glycation end-products; Akt, protein kinase B; IKK, IκB kinase; JNK, C-jun N-terminal kinase; MAPK, mitogen-activated protein kinase; NO, nitric oxide; PKC, protein kinase C; TGF-β, transforming growth factor.
cell proliferation and lipid and hyaluronate deposition in the renal matrix and inner medulla, all established contributors to kidney damage [6]. An additional possible mechanisms linking insulin resistance and kidney damage could be represented by salt sensitivity which characterizes patients with both type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) and microalbuminuria. In fact, Trevisan et al. have elegantly documented that patients with diabetes and microalbuminuria respond to an increased salt intake with an increase in blood pressure, glomerular pressure and albumin excretion. These features were strongly associated with insulin resistance, thus suggesting that abnormal salt sensitivity may underlie, at least partly, the deleterious effect of insulin resistance on renal function [7–8]. We should never forget that when taking into account the role of human insulin resistance in metabolic and haemodynamic abnormalities, it remains possible, though not demonstrated so far, that in some individuals, insulin resistance rather than being a systemic abnormality is specific for a subset of tissues or organs, thus being responsible for specific clinical consequences.

A new family of molecules, mainly, though not exclusively, secreted by adipose tissue (i.e. adipocytokine), have been linked to both insulin resistance and low-grade inflammation and, consequently, to endothelial dysfunction and vascular damage [9]. Among other effects, most adipocytokines inhibit insulin signalling at the insulin receptor and insulin receptor substrate level by several mechanisms including the modulation of kinases such as C-jun N-terminal kinase (JNK), IκB kinase (IKK) and specific PKC isoforms [10] (Figure 1). Most likely because of reduced renal metabolism, increased levels of many circulating adipocytokines parallel the glomerular filtration rate (GFR) decline thus, representing a potentially modifiable pathogenic mechanism of vascular disease in the presence of kidney dysfunction.

In this context, we would like to stress the controversial role of adiponectin whose tissue expression and serum levels can be modulated by insulin sensitizer drugs [9] and which, in contrast to most adipocytokines, exert a peculiar anti-atherogenic, anti-inflammatory and insulin-sensitizing effect [9].

Quite surprisingly, given its beneficial effect on insulin resistance, most studies [11–14] have revealed that circulating adiponectin concentrations are positively correlated with increased urinary albumin excretion (UAE) and negatively with GFR. Similar correlations were also observed among non-diabetic, untreated individuals [15], thus making it unlikely that findings from previous studies [12–14] were biased by diseases (i.e. diabetes and/or kidney disease) and treatments (i.e. statins, RAS inhibitors and thiazolinediones) known to affect circulating adiponectin levels. In addition, the latter data obtained mostly in healthy individuals [15] reinforce a previous hypothesis suggesting that the paradoxical increased levels of circulating adiponectin in kidney dysfunction, rather than being an effect of decreased renal metabolism, represent a homeostatic protective mechanism aimed at countering renal and cardiovascular damage [16].

Along this line are animal studies showing that adiponectin inhibits albuminuria and kidney fibrosis in the 5/6 nephrectomy adiponectin knock-out mice [17] and that adiponectin null mice [11] are characterized by albuminuria and podocyte foot process effacement which are reversed by administration of recombinant adiponectin.

In order to get deeper insights into the role of adiponectin in renal function, human studies aimed at targeting its circulating concentration are definitively needed. In addition, studies elucidating the pleiotropic effects of other adipocytokines would help explore new emerging pathways underlying kidney dysfunction.

Molecular mechanisms underlining the direct deleterious effect of insulin resistance on kidney function are only partially unravelled. In the course of insulin resistance, activation of the phosphatidylinositol-3-kinase (PI3K)/protein kinase B (Akt) pathway is affected while that of the mitogen-activated protein (MAP) kinase pathway is normal [18]. A natural genetic model of human insulin resistance [19] shows that, in endothelial cells, such unbalanced activation of insulin signalling causes reduction of Akt-dependent synthesis of nitric oxide (NO), a major vasodilator, and increased MAPK-dependent vaso-reactivity [20], two dysfunctions which may well act as promoters of both micro- and macro-vascular abnormalities (Figure 1).

(ii) The emerging role of podocyte

Podocytes help prevent proteinuria through a complex regulation of actin cytoskeleton in their foot processes. Decreased podocyte number and podocyte foot process effacement have been reported in diabetic patients with early phases of kidney damage [21]. Thus, the role of podocytes in diabetic kidney dysfunction has become the subject of intense research. It is of note in our specific context that the podocyte does express all elements of the insulin-signalling cascade and that its function, structure and survival are under the control of insulin stimulation [22]. Welsh et al. have recently reported that mouse models not expressing the podocyte insulin receptor develop podocytes apoptosis, effacement of its foot processes along with thickening of the glomerular basement membrane, increased glomerulosclerosis and albuminuria [23]. Conversely, in human podocytes insulin directly improves survival and induces the short-term reorganization of the actin cytoskeleton, eventually resulting in retraction of cellular processes and increased permeability [22]. Of interest, acute insulin infusion in normal subjects causes transient proteinuria [24], a finding compatible with the above reported effect of the hormone on podocytes. Finally, podocytes isolated from diabetic db/db mice, which develop an experimental model of kidney dysfunction, were unresponsive to insulin in terms of glucose metabolism [21], thus pointing to podocyte-specific insulin resistance as a potential mechanism of kidney damage (Figure 1).

Several evidence support the role of nephrin, a transmembrane signalling molecule able to prevent protein loss through maintenance of the slit diaphragm between adjacent podocyte foot processes, in podocyte-specific insulin resistance. Immortalized podocytes from two different patients with nephrin mutations were, in fact,
unresponsive to insulin stimulation of glucose uptake. Knocking nephrin down with siRNA in wild-type podocytes abrogated insulin action, while stable nephrin transfection of nephrin-deficient podocytes rescued their insulin response [25]. Thus, nephrin downregulation, which characterizes early phases of diabetic kidney dysfunction [26], could play a pathogenic role in kidney damage through the induction of podocyte insulin resistance. Finally, studies in adiponectin null mice also support the notion that podocyte function is under the control of insulin and insulin-sensitizing molecule [11].

Taken altogether, these data strongly suggest that podocyte insulin action is important for the overall glomerular function as well as for the podocyte morphology, cytoskeleton remodelling and, eventually, survival.

Most of the effects so far reported are believed to be operating on the glomerulus. As a matter of fact, although a role for the tubule in CKD, especially among diabetic patients, is increasingly recognized [27], recent data in animal models have shown that insulin resistance-related kidney damage is entirely due to glomerulus dysfunction [28]. Future studies will answer the question of whether or not this applies also to humans or whether, in contrast, insulin resistance affects the kidney function of some patients also through a deleterious effect on the tubule.

Association between insulin resistance and kidney dysfunction

(i) Evidence from non-genetic studies

In reviewing the available data on the association between these two abnormalities, we will use not only studies where insulin resistance was considered as exposure, but also those addressing the role of MetS. In fact, insulin resistance is a major factor predisposing to MetS [2] which can, therefore, be used as a reasonable equivalent of it.

Given the great number of papers published on this issue, only a few will be here discussed while all of them are listed in Supplementary data, Table S1.

**Studies in the general population and non-diabetic subjects.** In a large population-based cross-sectional study, Chen et al. described a 2.6 increased risk of CKD in individuals with MetS when compared with those without it [3]. MetS has been also reported to almost double the risk of microalbuminuria [3]. Similarly, a strict, independent association between insulin resistance, estimated by a frequently sampled intravenous glucose tolerance test, and microalbuminuria was described in non-diabetic subjects [29].

In a community based, prospective cohort of 10 096 middle-aged adults, the MetS was independently associated with a 43% increased risk of incident CKD [30]. A similar 55% increased risk for subjects with MetS has been described in a meta-analysis of prospective studies comprising a total of 301 46 individuals [31].

Studies in patients with T1DM. In a pioneering cross-sectional study in patients with T1DM, those with microalbuminuria were reported to be more insulin resistant and to have a more atherogenic profile than those with normoalbuminuria [32].

In two subsequent prospective studies, insulin resistance predicted both micro- [33] and macro- [34] albuminuria in patients with T1DM.

Furthermore, in 2415 patients with T1DM, the prevalence of MetS has been reported equal to 28, 44, 62 and 68% in individuals with normo-, micro-, macro-albuminuria and end-stage renal disease, respectively. Overall, patients with MetS had a 3.75-fold increased risk of kidney damage [35].

Finally, reduced insulin sensitivity characterizes non-diabetic parents of patients with T1DM and albuminuria [36]. This finding suggests a familial, probably genetic in nature, predisposition to insulin resistance that, in patients with T1DM increases the risk of developing kidney dysfunction [36].

Studies in patients with T2DM. Groop et al. first reported the association between insulin resistance and microalbuminuria in patients with T2DM [37]. We have recently reported in such patients a strong association of insulin resistance and the MetS with increased albuminuria [38] as well as between MetS and CKD, with a progressive drop of GFR according to the increasing number of MetS traits [39].

(ii) Evidence from genetic studies

Inferring causality from cross-sectional association studies is problematic. This is particularly true in the case of insulin resistance and kidney dysfunction. The latter condition is heavily associated with a constellation of metabolic abnormalities, (i.e. hypertension, dyslipidaemia, obesity and hyperglycaemia) which are totally superimposable to those characterizing insulin resistance, thus making it very difficult to propose a cause–effect relationship between the two conditions.

Genetic epidemiology can help establish causality between human phenotypes. In fact, a strong genotype–phenotype association implies a direct causal relationship. This is particularly true if, following epidemiological evidence, functional *in vitro* and *in vivo* studies, addressing the biology underlying the observed association, become available. So, if genetic variants which are established contributory causes of a given phenotype (i.e. trait A) are also associated with a different phenotype (i.e. trait B) proven to be related to trait A, one is allowed to infer causality, with trait A being pointed to as the causal variable.

Population and family studies have clearly indicated that in both T1DM and T2DM kidney dysfunction has a strong genetic basis [40]. Of note, in the specific context of this article, several genetic studies have reported the association between kidney dysfunction in diabetic individuals and variants of genes affecting insulin resistance and related networks, including abnormal insulin signaling, altered adipogenesis, adipocytokine dysregulation,
The common soil of metabolic and kidney abnormalities

low-grade inflammation and endothelial dysfunction. Only few of such data will be presented here as paradigms of the relationship between insulin resistance and kidney dysfunction in diabetic patients.

Ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1). Among the genes involved in the insulin-signalling pathway, is the transmembrane glycoprotein ectonucleotide pyrophosphatase phosphodiesterase 1 (ENPP1), which binds to and inhibits the insulin receptor and subsequent downstream insulin signalling and action in both cultured cells and animal models [19]. In addition, ENPP1 is over-expressed in tissues of insulin-resistant individuals [19]. Finally, in vitro studies have characterized the K121Q polymorphism (rs1805101) as a gain of function amino acid substitution with the less frequent Q121 variant being a stronger inhibitor of insulin signalling when compared with the prevalent K121 variant [19].

We have first reported that, among patients with T1DM and albuminuria, those carrying the ENPP1 Q121 variant had a faster rate of GFR decline over time [41]. An association between the ENPP1 KQ121Q and the reduced GFR was then reported in subsequent studies carried out in patients with both T1DM [42] and T2DM [43]. We acknowledge that no association between ENPP1 K121Q and kidney dysfunction has been reported in Danes with T1DM [44]. It is worth noting, however, that this is the same population in which no association is detectable between the Q121 variant and insulin resistance [45], thus making uncertain the study rationale. A possible mechanism accounting for such associations is the predisposing effect of this variant to insulin resistance-mediated atherosclerosis [46], an independent risk factor for renal dysfunction in diabetic patients. In addition, a direct deleterious role of the Q121 variant in human endothelial cell function [47] may also play a role in affecting kidney function.

Insulin receptor substrate 1. Insulin receptor substrate 1 plays a key role in insulin signalling and action in several tissues including kidney [20]. An IRS1 polymorphism, namely G972R (rs1801278), determines an amino acid substitution [48] with a loss of function of the protein. This polymorphism has been reported to play a role in susceptibility to insulin resistance [49] and T2DM [50–51]. Very recently, Thameem et al. [52] have described an association between IRS1 G972R polymorphism and kidney function in the San Antonio Family Diabetes/Gallbladder Study (SAFDGS), with R972 carriers showing a significantly decreased GFR. Unfortunately, this finding was not replicated in two independent family studies including the San Antonio family heart study and the Joslin study on the genetics of type 2 diabetes. The authors have also reported that insulin-induced phosphorylation of IRS1 and Akt is reduced in mesangial cells expressing the R972 variant when compared with cells expressing the wild-type G972 variant [52]. Although these new findings are certainly compatible with the hypothesis of a direct role of insulin resistance in kidney dysfunction, the observed association needs to be confirmed in further, possibly larger, studies before to consider as established.

PPARγ. Among genes involved in adipogenesis and adipose tissue metabolism is peroxisome proliferator-activated receptor gamma (PPARγ), a member of the nuclear hormone receptor superfamily of ligand-activated transcription factors which plays a key role in regulating the expression of numerous genes. Although the molecular mechanism remains elusive, the P12A polymorphism (rs1801282) located in the PPARγ2 isoform has been associated with enhanced insulin sensitivity and a significantly reduced risk of T2DM [53], with A12 representing the protective variant. Two cross-sectional studies have first reported that, among patients with T2DM, those carrying the A12 variant (i.e. PA or AA genotype) are at reduced risk of kidney dysfunction when compared with PP patients [54–55]. We have recently reported that among 1119 hypertensive patients with T2DM and normoalbuminuria, A12 carriers had a 55% reduction of developing incident microalbuminuria, when compared with PP individuals [56]. Finally, a recent meta-analysis comprising a total of 6564 patients with T2DM has confirmed a protective effect of the A12 variant on albuminuria [57].

Besides the candidate gene approach, since 2005 great effort has been employed to unravel the genetic component(s) of complex phenotypes by genome-wide association studies (GWAS) [58–60].

Variants in the ~20 loci have been reported by GWAS as established markers (i.e. genome-wide statistical significance with P < 5 × 10−8) of GFR and kidney dysfunction in the general population [61]. Of note, one of these loci, namely the glucokinase regulator whose product inhibits hepatic glucokinase, has been firmly reported also as a marker of insulin resistance, as indicated by its association at genome-wide statistical significance with the homeostatic model assessment of insulin resistance index [62], fasting insulin [62] and MetS [63]. This observation reinforces the hypothesis that insulin resistance might be pathogenic for kidney dysfunction. Unfortunately, none of the six GWAS-derived loci which have been robustly associated with kidney dysfunction in diabetic patients has achieved genome-wide statistical significance, thus stressing the yet preliminary status of these results [61].

Although data from both candidate and GWAS-derived genes have contributed to shedding light on the genetics of kidney failure, a full comprehension of the molecular pathogenesis underlying it, including the role of insulin resistance genes, is still to come. Advances in technology, such as massively parallel gene sequencing and characterization of alternative modes of inheritance, are likely to be instrumental in further elucidating the genetic architecture of kidney dysfunction.

Insulin-sensitizing treatment and kidney function

The best approach to definitively answer the question of whether insulin resistance is pathogenic for kidney dysfunction is to conduct intervention studies able to improve
insulin sensitivity and then to assess whether this is paralleled by a concomitant improvement of kidney function. A small elegant study showed that, when compared with the placebo group, patients with T2DM treated for 3 months with rosiglitazone, a thiazolidinedione with insulin-sensitizing effect, had improved insulin sensitivity, increased serum adiponectin concentration and reduced UAE [64]. Given the possible beneficial effect of adiponectin in preventing proteinuria, it is entirely possible that changes in circulating adiponectin levels have mediated, at least partly, the positive effect of rosiglitazone on albuminuria observed in this study.

A recent meta-analysis of 15 double-blind, randomized, studies in patients with T2DM has confirmed a positive role of thiazolidinediones on urinary albumin and total protein excretion [65]. A subsequent study [66] in 4351 drug-naïve patients with T2DM has confirmed that rosiglitazone monotherapy delays the rise of albumin/creatinine ratio when compared with metformin and preserves the GFR when compared with glyburide. These results are encouraging and reinforce the belief that insulin resistance is the pathogenic factor for kidney dysfunction. Conversely, we would like to acknowledge that several other mechanisms, such as reduction of low-grade chronic inflammation, inhibition of TGF-β and other growth factors renal expression as well as of glomerular and tubular cell proliferation and attenuation of the decrease in matrix metalloproteinase processes, can also contribute to the beneficial effect of thiazolidinediones on kidney function [67].

Finally, a number of studies in obese patients with proteinuric nephropathies have shown that body weight reduction induced by low-calorie diets, physical exercise or bariatric surgery is paralleled by a significant reduction of proteins loss. Such renoprotective effect can be easily explained by changes in a number of metabolic and hemodynamic pathways which are mostly related to the well-known insulin sensitivity improvement invariably determined by any intervention able to induce weight loss [68].

**Conclusions**

The prevalence of kidney dysfunction is increasing worldwide as is that of insulin resistance and related abnormalities which, through mechanisms involving both systemic and local effects, are the pathogenic factors for renal failure. This relationship is based upon strong epidemiological evidence, addressing the association of kidney dysfunction with both genetic and non-genetic markers of insulin resistance. Also intervention studies aimed at reversing insulin sensitivity in patients with T2DM, though preliminary, point to insulin resistance as a pathogenic factor for kidney dysfunction. Trials exploring hard renal end-points, designed to investigate whether treating insulin resistance prevents kidney function worsening and/or represents an efficient and tailored therapy for patients with established kidney dysfunction, would be opportune and are, therefore, welcome.

**Supplementary data**

Supplementary data are available online at http://ndt.oxfordjournals.org.

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Aldosterone synthase inhibition in humans

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Abstract

Aldosterone synthase (CYP11B2) inhibition has emerged as a new option for the treatment of hypertension, heart failure and renal disorders, in addition to mineralocorticoid receptor (MR) blockade. The aim is to decrease aldosterone concentrations in both plasma and tissues, thereby decreasing MR-dependent and MR-independent effects in the cardiac, vascular and renal target organs. LC1699 was the first orally active aldosterone-synthase inhibitor to be developed for human use. Its structure is similar to that of FAD286, the dextroenantiomer of the inhibitor to be developed for human use. Its structure is similar to that of FAD286, the dextroenantiomer of the inhibitor to be developed for human use.

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