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Comorbidities in type 2 diabetes mellitus patients with neurosyphilis

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Comorbidities in type 2 diabetes mellitus patients with neurosyphilis

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Comorbidities in type 2 diabetes mellitus patients with neurosyphilis

Running title: Neurosyphilis in type 2 diabetic patients

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ABSTRACT

Type 2 diabetes (T2D) affects approximately 350 million people worldwide. This disease is associated with several vascular complications and with an increased risk of infection. In turn, infections can increase the risk of complications in these patients. Syphilis is a sexually transmitted infection with a highly variable clinical presentation. Case reports of T2D patients with syphilis describe unusual presentations of this infection. The effect of the different stages of syphilis upon T2D complications, however, remains uncertain. We aimed to understand this effect by comparing data from all hospitalized T2D patients between those with neurosyphilis (NS) and those without associated diagnosis of syphilis concerning the frequency of such complications. Certain variables were compared with hospitalized syphilitic T2D patients with stages other than NS. We found an increased prevalence of diabetic neuropathy, nephropathy, and ischemic cerebrovascular disease in patients with NS. Ischemic heart disease, however, was less prevalent in patients with NS than in those without the diagnosis of syphilis. These findings could provide clues to our understanding of syphilis and its influence upon T2D complications. Furthermore, if NS can be detected and treated in T2D patients, additional burden could be eliminated.

Diabetes mellitus comprises a group of endocrine diseases characterized by hyperglycemia due to impaired glucose metabolism. In type 1 diabetes, damage to the β-cells leading to a decrease in insulin production constitutes the basis of this disease, whereas most cases of type 2 diabetes (T2D) are associated with a loss of sensitivity to this hormone (1). T2D represents the vast majority of global diabetes mellitus burden, afflicting an estimated 350 million people (2). This condition is associated with several serious complications, including ischemic heart disease, cerebrovascular disease, peripheral vascular disease, as well as diabetic nephropathy, neuropathy and retinopathy. Afflicted patients also have an increased risk of respiratory, urinary, cutaneous and mucosal infections; this is believed to result from a compromise in lymphocyte function and granulocyte response, with subsequent impairment in chemotaxis, adhesion, and phagocytosis (3-5).

Infections themselves promote the risk of complications in T2D patients, such as nephropathy and acute kidney injury (6; 7). T2D and infections can thereby exert an influence on the course of each other. One of such infections might be syphilis, a sexually transmitted disease caused by *Treponema pallidum* that can present as a plethora of signs and symptoms (8). Several studies have reported cases of concomitant T2D and syphilis, although the relationship between these two diseases is not yet clearly understood. Neurosyphilis (NS) can damage the hypothalamus-pituitary axis (9), and it has been suggested that this facilitates the onset of T2D (10); conversely, T2D may have an immunosuppressive effect that promotes the development of NS in patients infected with *T. pallidum* (10). Furthermore, case reports describing T2D patients with *lues maligna* and syphilitic optic neuropathy, manifestations of syphilis normally associated with immunocompromised patients, were published (11-13). One case report described acute-onset hemichorea as the first

manifestation of NS in a T2D patient (14). Another study reported a case of *status epilepticus*, and proposed that this condition was the result of a synergism between NS and T2D hyperglycemia (15).

Nevertheless, the alleged effect that syphilis may have upon T2D complications remains unclarified. We aimed to characterize hospitalized T2D patients with NS (particularly concerning demographic and clinical characteristics, length of hospital stay and in-hospital mortality) and to compare such data with that from hospitalized T2D patients without the diagnosis of syphilis.

RESEARCH DESIGN AND METHODS

Subjects and Study Design

We used the database provided by Administração Central do Sistema de Saúde (Central Administration of the Health System; ACSS) containing a registry of all diabetes mellitus hospitalizations that occurred in mainland Portugal public hospitals from January 2000 to December 2014; n=1,663,162. Each episode was assigned a main diagnosis (clinical entity responsible for the patient hospitalization) and up to 19 accompanying diagnoses classified according to the International Classification of Diseases 9, Clinical Modification (ICD-9-CM) codes. Each hospitalization also had ICD-9-CM codes for up to 20 procedures performed. We excluded hospitalizations without information about sex and with age inferior to 1 year or superior to 115 years (15 and 124 cases were excluded, respectively). Afterwards, we selected all hospitalizations with a main or accompanying diagnosis of T2D, which was defined by the of ICD-9-CM codes 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82,

250.90, 250.92; n=1,576,374. Any remaining hospitalization with the diagnosis of type 1 diabetes, identified by the ICD-9-CM codes 250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93 was afterwards excluded (1,013 cases were excluded). Among the 1,575,361 remaining hospitalizations, those with the associated diagnosis of syphilis were identified by the ICD-9-CM codes 090.x-097.x, and those with the diagnosis of NS in particular were identified by the ICD-9-CM code 094.x. Any hospitalization with the diagnosis of syphilis occurring from 2000 to 2014 was analyzed, whereas hospitalizations without this diagnosis prior to 2010 were excluded (840,643 cases were excluded); n=734,718.

We then restructured the data, matching hospitalizations by birthdate, sex, town, and an anonymous identifier. Such restructuring step allowed us from now on to work with patient data as opposed to hospitalization data; n=510,118 patients.

Afterwards, we elected 3 study groups from our population of patients: one group of patients with NS (n=260 patients), one control group of those without the diagnosis of syphilis (henceforth referred to as the non-syphilitic population; n=509,183 patients) and, within this patient group, a control subset of patients submitted to LP (n=4,589 patients). Hospitalizations corresponding to patients submitted to LP were identified by the ICD-9-CM code 03.31.

The 3 studied groups were compared concerning demographic characteristics (age and gender), in-hospital mortality and hospital length of stay (in order to compare length of stay across the 3 groups, we used hospitalization data). Comorbid conditions compared (and their respective ICD-9-CM codes) included arterial hypertension (401.1, 401.9, 402.1, 402.9,

404.1, 404.9, 405.1, 405.9), hyperlipidemia (272.0-272.4), atrial fibrillation (427.31), obesity (278.0), smoking history (V15.82, 305.1) and Human Immunodeficiency Virus (HIV) disease (042). Complications assessed (and their associated ICD-9-CM codes) included diabetic nephropathy (250.4, 583.81), neuropathy (250.6, 357.2), and retinopathy (250.5, 362.0), ischemic heart disease (410.x-414.x), ischemic cerebrovascular disease (433.x-435.x), hemorrhagic cerebrovascular disease (430.x-432.x) and peripheral vascular disease (440.x, 443.x- 445.x, 557.x).

Lastly, certain variables found to be significantly associated with the diagnosis of NS were compared (within our syphilitic population; n=935) between patients with NS and those with other stages of syphilis (n=675). Such variables were also compared between the syphilitic T2D patients without NS and the non-syphilitic T2D population. One variable was compared within the non-syphilitic population between the LP subset and the remaining patients. Definitions of the different stages of syphilis were based on the European Center for Disease Prevention and Control criteria. The study design process is illustrated in a flowchart (Figure 1).

Statistical Analyses

Descriptive statistics were used to compare demographic and clinical characteristics of the 3 studied groups. Data was expressed as absolute frequencies and percentages for categorical variables and as medians and interquartile ranges for continuous variables. Categorical variables were analyzed using the chi-square test or Fisher's exact test, whereas continuous variables were compared using Mann-Whitney U test; p values < 0.050 were considered statistically significant. We performed binomial logistic regression analysis with diabetic and cardiovascular complications and in-hospital mortality as outcomes, adjusting for age, sex

and comorbid conditions (conditions with $p < 0.200$ were included in the multivariable model). This logistic regression analysis was performed to estimate the strength of association of between occurrence of each outcome and the presence of an associated diagnosis of NS. All statistical analysis of data was performed using SPSS version 23.0 (SPSS, Inc., Chicago, IL).

RESULTS

Between 2000 and 2014, we found 297 hospitalizations corresponding to 260 T2D patients with NS. From 2010 to 2014, there were 733,930 hospitalizations corresponding to 509,183 T2D patients without the diagnosis of syphilis. Among these, 4,589 patients were submitted to LP. Regarding hospitalizations without associated diagnosis of syphilis, cerebral artery occlusion was the main diagnosis in 6.2% those in which LP was performed and in 2.6% of the remainder.

Demographic characteristics

The percentage of males was significantly higher in patients with NS (71.9%) than in the non-syphilitic population (49.6%) and the LP subset (51.6%) (Table 1). The median age was significantly lower in patients with NS (65.0 years) than in non-syphilitic patients (73 years) and in the LP subset (71 years) (Table 1). Hospitalizations with the diagnosis of NS were significantly longer than those without the diagnosis of syphilis (median of 14 days and an interquartile range of 8 to 26 days *versus* a median of 5 days and an interquartile range of 1 to 11 days; $p<0.001$). However, no significant difference was found between the length of hospitalizations with the diagnosis of NS and those without the diagnosis of syphilis in which

LP was performed (median of 14 days and an interquartile range of 8 to 26 days *versus* 13 days and an interquartile range of 7 to 24 days; p=0.095).

Comorbid conditions

HIV disease was significantly more prevalent among patients with NS (8.8%) than in the non-syphilitic population (0.2%) and in the LP subset (2.6%) (Table 1). Patients with NS had significantly lower frequencies than the non-syphilitic population and the LP subset in regard to arterial hypertension (55.4% *versus* 63.9% and 66.2%, respectively), atrial fibrillation (8.5% *versus* 14.3% and 13.4%, respectively) and obesity (7.3% *versus* 15.7% and 14.1%, respectively) (Table 1). Patients with NS, when compared with the LP subset, also had a significantly lower frequency of hyperlipidemia (28.8% *versus* 35.8%) (Table 1). However, the prevalence of hyperlipidemia did not differ between patients with NS and the total amount of non-syphilitic patients (Table 1). The prevalence of smoking history did not differ significantly among the 3 study groups (Table 1).

Adjusted comorbid conditions

The prevalence of atrial fibrillation did not differ between the 3 study groups when adjusted for age. Odds ratio (OR) for the NS group was 0.809 (95% CI: 0.517-1.264; p=0.351) when compared with the non-syphilitic population and 0.780 (95% CI: 0.494-1.230; p=0.285) when compared with the LP subset. The prevalence of arterial hypertension did not differ between the NS group and the non-syphilitic population when adjusted for age and sex, but it remained significantly lower in the NS group than in the LP subset. OR for the NS group was 0.783 (95% CI: 0.612-1.000; p=0.050) when compared with the non-syphilitic population and 0.756 (95% CI: 0.584-0.978; p=0.033) when compared with the LP subset.

When adjusted for age and sex, the prevalence of hyperlipidemia did not differ between the NS group and the LP subset; OR for the NS group was 0.759 (95% CI: 0.576-1.002; p=0.052). After adjustment for age and sex, the prevalence of obesity remained significantly lower in the NS group than in the non-syphilitic population and the LP subset. OR for the NS group was 0.374 (95% CI: 0.233-0.599; p<0.001) when compared with the non-syphilitic population and 0.472 (95% CI: 0.291-0.764; p=0.002) when compared with the LP subset.

Outcomes

Ischemic cerebrovascular disease was significantly more frequent in NS patients (17.3%) than in the non-syphilitic population (8.0%), but not when compared with the LP subset (Table 1). Diabetic neuropathy was significantly more prevalent in NS patients (9.2%) than in non-syphilitic patients (1.8%) or in the LP subset (4.8%) (Table 1). Conversely, NS patients had a significantly lower prevalence of ischemic heart disease (9.6% *versus* 18.0% in the non-syphilitic population); this difference was not confirmed when the NS group was compared with the LP subset (Table 1). In-hospital mortality was significantly lower in NS patients when compared with the LP subset (10.8% *versus* 17.1%), but not when compared with all non-syphilitic patients (Table 1). Frequency of hemorrhagic cerebrovascular disease, peripheral vascular disease, diabetic nephropathy and retinopathy did not differ when comparing the 3 study groups (Table 1).

Adjusted outcomes

After adjustment by binomial logistic regression, diabetic neuropathy remained significantly associated with the presence of NS (Tables 2 and 3). Comparing the NS group with all non-syphilitic patients, ischemic cerebrovascular disease remained significantly associated with

the presence of NS, whereas ischemic heart disease remained significantly associated with the absence of NS (Table 2). Diabetic nephropathy, previously unassociated with significant p values, became significantly associated with the presence of NS after adjustment (Table 2). Comparing the NS group with the LP subset, in-hospital mortality remained significantly associated with the absence of NS (Table 3). All remaining complications that were found to show no statistical significant associations among the 3 study groups remained as such after adjustment (Tables 2 and 3).

Within our non-syphilitic population, the prevalence of ischemic heart disease was significantly lower in patients submitted to LP than in patients not submitted to this procedure (13.7% *versus* 18.1%; $p<0.001$). This association remained significant when adjusted for age, sex, and HIV disease; OR for patients submitted to LP was 0.730 (95% CI: 0.671-0.795; $p<0.001$).

Comparison with other syphilis stages

Within our syphilitic population, the prevalence of diabetic neuropathy was significantly higher among patients with NS than in those with other stages of syphilis (9.2% *versus* 4.7%) (Table 4). The prevalence of diabetic nephropathy did not differ between patients with NS and those with other stages of syphilis (Table 4). The prevalence of ischemic heart disease was significantly lower in patients with NS than in those with other stages of syphilis (9.6% *versus* 19.1%) (Table 4).

Comparing the syphilitic patients with stages other than NS with the non-syphilitic population, the former had a significantly higher prevalence of diabetic neuropathy (4.7% *versus* 1.8%) and nephropathy (12.3% *versus* 7.8%) (Table 4). The prevalence of ischemic

heart disease did not differ between syphilitic patients without NS and the non-syphilitic population (Table 4). Significant associations remained as such after adjustment for age, sex and HIV disease (Tables 5 and 6).

DISCUSSION

Study groups

Since hospital readmissions can be frequent, analyzing hospitalization data could result in overestimation of certain conditions. In our database, hospitalizations from 2010 onwards had an identifier which allowed the accurate anonymous identification of a patient. To avoid analysis of repeated cases, we selected these hospitalizations and restructured them into patient data based on the anonymous identifier and certain demographic characteristics. Since syphilis has a reduced prevalence in Portugal (1,016 cases reported between 2011 and 2014 (16)), admissions with this diagnosis sharing the same demographic data likely represent the same patient. Therefore, in order to maximize the number of cases, we selected all T2D hospitalizations with diagnosis of syphilis, regardless of the presence of an anonymous identifier. We designed a control group of T2D patients without diagnosis of syphilis, reducing the possibility of undiagnosed NS cases among patients with *T. pallidum* infection. Within this group, the LP subset shares a similar diagnostic workup with the NS group, yet differs in regards to the presence of *T. pallidum* in the central nervous system (CNS), allowing for a more specific comparison.

Demographic characteristics and comorbid conditions

In our study, NS patients were younger than the non-syphilitic population, which may explain the lower prevalence of atrial fibrillation in the former. Age and gender differences may

account for the lower prevalence of arterial hypertension among patients with NS. However, the lower prevalence of obesity in the NS group was not explained by these differences. The relationship between obesity and some infections can be complex, with each condition potentially promoting the other (17). However, no association between NS and obesity that we know of has been previously described in the literature. The longer length of hospital stay among admissions with the diagnosis of NS may reflect the management of this condition, which frequently requires hospitalization, with administration of intravenous penicillin for 10-14 days (18).

Outcomes

Diabetic neuropathy

Diabetic neuropathy affects the peripheral nervous system (19), while NS is mainly a disease of the CNS (20). It is intriguing that we found an increased prevalence of this complication among NS patients. This increase could be the result of misdiagnosis. For instance, patients with NS affecting certain CNS structures, can have sensitive impairment (20), and this might be mistaken with diabetic neuropathy. On the other hand, patients with NS might have *T. pallidum* invasion of tissues other than those of the CNS (20). Diabetic neuropathy can be caused by ischemia of the vasa nervosa, and *T. pallidum* is known to produce endarteritis of the vasa vasora of certain vessels (21). It is possible that *T. pallidum* could cause endarteritis of the vasa nervosa of certain nerves, producing neuropathy. Such neuropathy could be confused with diabetic neuropathy, erroneously increasing the prevalence of this complication. Nevertheless, other possibilities could explain the observed increase. NS could induce a CNS lesion that facilitates the development of diabetic neuropathy. In addition, it has been suggested that NS can be caused by distinct, more neuroinvasive strains of *T.*

pallidum (22); some attribute specific to such strains could promote the onset of diabetic neuropathy (20). To understand whether the increase in diabetic neuropathy was exclusive to NS, we compared the prevalence of this complication between our non-syphilitic population and patients with syphilis stages other than NS. We found a higher frequency of diabetic neuropathy among the syphilitic patients without NS, which suggests a role for the other stages of syphilis. The peripheral nerves of syphilitic T2D patients could be the target of both hyperglycemia and spirochetemia, with syphilis hastening the onset of diabetic neuropathy. Next, to ascertain the plausibility of an additional synergic mechanism from NS, we analyzed the prevalence of this complication within the syphilitic T2D population. We found a higher prevalence in patients with NS than in those with other stages of syphilis, which suggests an additional contribution from this condition.

Diabetic nephropathy

As was the case with diabetic neuropathy, diabetic nephropathy was more prevalent not only in NS patients (after adjustment), but also in the other syphilitic patients, when compared with the non-syphilitic population. However, this prevalence did not differ between patients with NS and those with other stages of syphilis. Diabetic nephropathy is caused by the disruption of the glomeruli through several factors, including hyperglycemia (23). Such disruption can manifest as changes in the thickness and charge of the glomerular basement membrane, as well as mesangial sclerosis (23). Syphilis can lead to glomerular subepithelial deposition of immune complexes containing treponemal antigens, promoting the development of membranous glomerulonephritis (23). Although the kidney lesions produced by these conditions are different, both may manifest as a nephrotic syndrome (23). Thus, syphilitic membranous glomerulonephritis could be mistaken for diabetic nephropathy.

Nonetheless, a true synergistic association between the metabolic effects of T2D and the treponemal immune complexes might act upon the glomeruli, potentially accelerating the development of diabetic nephropathy.

Ischemic heart disease

Interestingly, we found a lower prevalence of ischemic heart disease in patients with NS than in non-syphilitic patients. This lower prevalence was not observed in the other stages of syphilis. Cardiovascular syphilis is associated with endarteritic processes of several structures, including the coronary arteries (21). Syphilitic disease of the coronary arteries affects mostly the ostia and proximal segments (21). As the endarteritis narrows the coronary lumen, ischemic heart disease may appear (21). The proximal involvement of the arteries can compromise large portions of the myocardium and result in sudden death (21). Other acute and chronic infections in general can aggravate the risk of coronary disease through changes in the metabolism, hemostasis and endothelial function (24; 25). There may be an exception in the case of hepatitis C, with one study suggesting a protective effect, potentially through a lipidemia-lowering mechanism secondary to liver damage (26). Nonetheless, to our knowledge, a protective effect of NS upon ischemic heart disease has not been described previously in the literature. The seemingly protective effect of NS presented here was unrelated to differences in age, sex and certain comorbid conditions. However, we must consider the possibility of an unaccounted-for confounding factor or bias. Such factors could be related to comorbidities in CNS pathology, as the LP subset also showed a lower prevalence of ischemic heart disease than the remaining non-syphilitic population, and no statistical difference was seen between the NS group and the LP subset. If this effect is indeed real, some characteristic of NS, such as specific *T. pallidum* strains, could be responsible.

Other outcomes

The higher prevalence of ischemic cerebrovascular disease among the NS group *versus* the non-syphilitic population is consistent with the deleterious effect of *T. pallidum* on the CNS (20). The endarteritis of the vasa vasora caused by *T. pallidum* can affect the vessels of the CNS, leading to the narrowing of their lumina (20). Since patients in the LP subset have a high burden of cerebral artery occlusion, this may explain the absence of difference in ischemic cerebrovascular disease and the increased in-hospital mortality when compared to the NS group.

Limitations and strong points

We consider of relevance to stress the limitations inherent to our study. Our study is data-centered, not patient-centered. Since we used an administrative database, the possibility of under-coding must be considered. In addition, hospitalizations with NS do not encompass all cases of this condition, especially asymptomatic variants. Furthermore, our analysis did not establish a temporal sequence between NS and the outcomes, which hinders the inference of a causal relationship. Regarding the non-syphilitic patients, we must acknowledge the possibility of false negative cases within this group. Since most patients with NS are asymptomatic, the misdiagnosis rate can be high (27). Concerning the LP subset, the burden of CNS pathology may confound some of the findings when it is compared with the NS group.

However, the population size is a strong point of our study. From 2000 to 2014, the incidence of hospitalizations with the diagnosis of acquired syphilis in mainland Portugal varied between 4.75 and 7.73 per 100,000 inhabitants (28). Assuming that these values could apply

to our non-syphilitic group, the high sample size would likely overshadow any potential effect due to false negative cases. Furthermore, assuming that there were undiagnosed cases of syphilis in our non-syphilitic population, this fact would not weaken the statistical power of the study. Instead, such fact would imply that, despite being compared with a control group containing undiagnosed cases of syphilis, our NS group still demonstrates significant associations with certain variables. To our knowledge, this is the first study undertaken to analyze the interaction between NS and T2D outcomes.

Conclusions

As the incidence of syphilis is increasing, this disease once again becomes quite relevant in clinical practice (8). Our study shows that T2D patients affected by NS exhibit increased morbidity. By promptly identifying and treating these patients, the additional burden could be prevented and alleviated. The clinician should thus be alerted to the possibility of this diagnosis. Additionally, our study raises several questions regarding the pathophysiology of syphilis and its relation with T2D. Do T2D patients with syphilis have augmented damage to certain structures due to a synergism of these conditions? Is there a pathophysiologic process in these patients that could account for the reduced prevalence of ischemic heart disease? This study paves the way for further investigations, particularly clinical prospective studies.

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Figure Legends

Figure 1. Flowchart illustrating the study population selection process. DM, diabetes mellitus; T2D, type 2 diabetes; T1D, type 1 diabetes; LP, lumbar puncture.

Table 1. Demographic and clinical characteristics of 509,443 type 2 diabetes patients

Characteristic	NS (N=260)	No syphilis Dx (N=509,183)	P value	No syphilis Dx, submitted to LP (N=4,589)	P value
Male sex – no. (%)	187 (71.9)	252,525 (49.6)	**<0.001**	2,370 (51.6)	**<0.001**
Age (years)	65.0 (55.0-74.0)	73.0 (64.0-80.0)	**<0.001**[*]	71 (63.0-58.0)	**<0.001**[*]
In-hospital mortality – no. (%)	28 (10.8)	55,288 (10.9)	0.963	783 (17.1)	**0.008**
Comorbid conditions – no. (%)					
Arterial hypertension	144 (55.4)	325,189 (63.9)	**0.004**	3,037 (66.2)	**<0.001**
Atrial fibrillation	22 (8.5)	72,883 (14.3)	**0.007**	616 (13.4)	**0.021**
Hyperlipidemia	75 (28.8)	162,286 (31.9)	0.295	1,643 (35.8)	**0.023**
Obesity	19 (7.3)	80,134 (15.7)	**<0.001**	646 (14.1)	**0.002**
Smoking history	28 (10.8)	41,785 (8.2)	0.132	413 (9.0)	0.334
HIV disease	23 (8.8)	1,130 (0.2)	**<0.001**[‡]	118 (2.6)	**<0.001**
Complications – no. (%)					
Ischemic heart disease	25 (9.6)	91,749 (18.0)	**<0.001**	628 (13.7)	0.061
Ischemic cerebrovascular disease	45 (17.3)	40,677 (8.0)	**<0.001**	827 (18.0)	0.771
Hemorrhagic cerebrovascular disease	6 (2.3)	7,099 (1.4)	0.184[†]	175 (3.8)	0.213
Peripheral vascular disease	15 (5.8)	30,441 (6.0)	0.887	262 (5.7)	0.968
Diabetic nephropathy	28 (10.8)	39,840 (7.8)	0.077	446 (9.7)	0.579
Diabetic neuropathy	24 (9.2)	8,913 (1.8)	**<0.001**[†]	221 (4.8)	**0.002**
Diabetic retinopathy	25 (9.6)	42,759 (8.4)	0.479	363 (7.9)	0.324

Age is shown as median and interquartile range. P values in each group, representing the comparison between that group and the NS group, were obtained with the chi-square test unless otherwise specified. [*]Mann-Whitney U test. [†]Fisher's exact test. Dx, Diagnosis; HIV, human immunodeficiency virus; LP, lumbar puncture; NS, neurosyphilis.

Table 2. Odds ratio (OR) comparison of cardiovascular and diabetic complications in type 2 diabetes patients with NS and those without diagnosis of syphilis

Complication	NS crude OR (95% CI)	P value	NS adjusted* OR (95%)	P value
Ischemic heart disease	0.484 (0.320-0.731)	**0.001**	0.504 (0.331-0.769)	**0.001**
Ischemic cerebrovascular disease	2.411 (1.748-3.325)	**<0.001**	2.981 (2.145-4.143)	**<0.001**
Hemorrhagic cerebrovascular disease	1.671 (0.743-3.755)	0.214	1.780 (0.789-4.013)	0.165
Peripheral vascular disease	0.963 (0.572-1.622)	0.887	0.931 (0.550-1.575)	0.790
Diabetic nephropathy	1.422 (0.960-2.105)	0.079	1.523 (1.020-2.276)	**0.040**
Diabetic neuropathy	5.708 (3.749-8.691)	**<0.001**	5.170 (3.382-7.904)	**<0.001**
Diabetic retinopathy	1.160 (0.768-1.753)	0.479	1.017 (0.669-1.546)	0.937
In-hospital mortality	0.991 (0.669-1.467)	0.963	1.216 (0.810-1.827)	0.345

HIV, human immunodeficiency virus.*Adjusted for: age, sex, arterial hypertension, atrial fibrillation, obesity, smoking history and HIV disease.

Table 3. Odds ratio (OR) comparison of cardiovascular and diabetic complications in type 2 diabetes patients with NS and those without diagnosis of syphilis submitted to LP

Complication	NS crude OR (95% CI)	P value	NS adjusted* OR (95%)	P value
Ischemic heart disease	0.671 (0.441-1.022)	0.063	0.736 (0.479-1.131)	0.162
Ischemic cerebrovascular disease	0.952 (0.684-1.324)	0.771	1.126 (0.803-1.579)	0.492
Hemorrhagic cerebrovascular disease	0.596 (0.261-1.358)	0.218	0.593 (0.259-1.359)	0.217
Peripheral vascular disease	1.011 (0.592-1.728)	0.968	1.021 (0.593-1.760)	0.940
Diabetic nephropathy	1.121 (0.748-1.679)	0.579	1.147 (0.757-1.739)	0.518
Diabetic neuropathy	2.010 (1.293-3.124)	**0.002**	1.865 (1.188-2.928)	**0.007**
Diabetic retinopathy	1.238 (0.809-1.896)	0.325	1.184 (0.767-1.827)	0.446
In-hospital mortality	0.587 (0.393-0.875)	**0.009**	0.605 (0.402-0.910)	**0.016**

LP, lumbar puncture; HIV, human immunodeficiency virus. *Adjusted for: age, sex, arterial hypertension, atrial fibrillation, hyperlipidemia, obesity and HIV disease.

Table 4. Comparison of cardiovascular and diabetic complications between type 2 diabetes patients with NS, those with other stages of syphilis, and those without diagnosis of syphilis

Complication	NS (N=260)	P value	Syphilis other than NS (N=675)	No diagnosis of syphilis (N=509,183)	P value
Diabetic nephropathy - no (%)	28 (10.8)	0.518	83 (12.3)	39,840 (7.8)	**<0.001**
Diabetic neuropathy - no (%)	24 (9.2)	**0.010**	32 (4.7)	8,913 (1.8)	**<0.001**
Ischemic heart disease - no (%)	25 (9.6)	**<0.001**	129 (19.1)	91,749 (18.0)	0.461

The p values in each group represent the comparison between that group and the group of patients with syphilis other than NS, and were obtained with the chi-square test. NS, neurosyphilis.

Table 5. Odds ratio comparison of cardiovascular and diabetic complications in type 2 diabetes patients with NS and those with other stages of syphilis

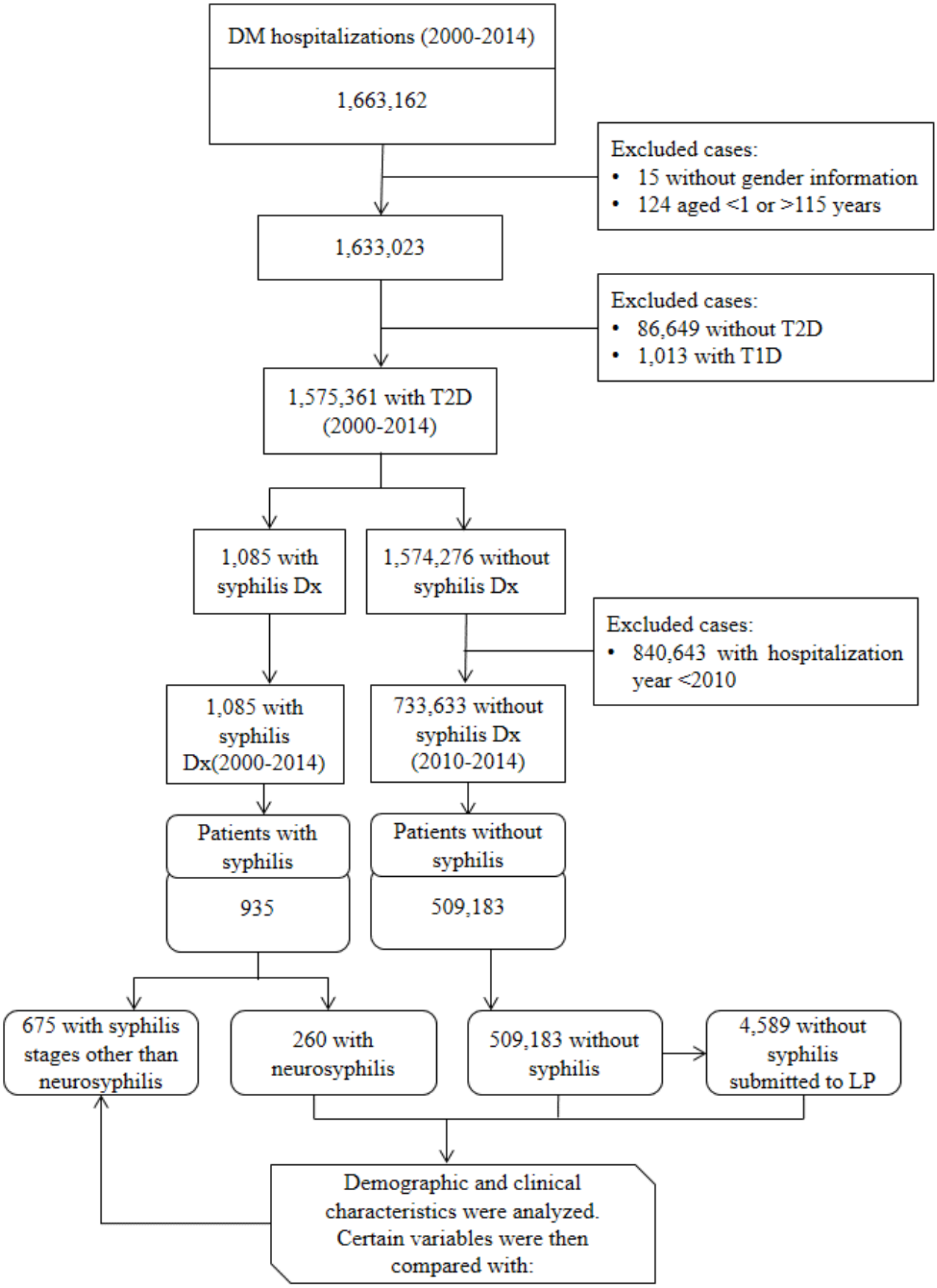
Complication	NS adjusted* odds ratio (95% CI)	P value
Ischemic heart disease	0.467 (0.294-0.739)	**0.001**
Diabetic neuropathy	1.949 (1.114-3.409)	**0.019**

NS, neurosyphilis; HIV, human immunodeficiency virus. *Adjusted for: age, sex and HIV disease.

Table 6. Odds ratio comparison of cardiovascular and diabetic complications in type 2 diabetes patients with stages of syphilis other than NS (OS) and those without diagnosis of syphilis

Complication	OS adjusted* odds ratio (95% CI)	P value
Diabetic nephropathy	1.660 (1.317-2.093)	**<0.001**
Diabetic neuropathy	2.526 (1.768-3.611)	**<0.001**

NS, neurosyphilis; HIV, human immunodeficiency virus. *Adjusted for: age, sex and HIV disease.


DM hospitalizations (2000-2014)
1,663,162
Excluded cases:
• 15 without gender information
• 124 aged <1 or >115 years
1,633,023
Excluded cases:
• 86,649 without T2D
• 1,013 with T1D
1,575,361 with T2D (2000-2014)
1,085 with syphilis Dx
1,574,276 without syphilis Dx
Excluded cases:
• 840,643 with hospitalization year <2010
1,085 with syphilis Dx(2000-2014)
733,633 without syphilis Dx (2010-2014)
Patients with syphilis
935
Patients without syphilis
509,183
675 with syphilis stages other than neurosyphilis
260 with neurosyphilis
509,183 without syphilis
4,589 without syphilis submitted to LP
Demographic and clinical characteristics were analyzed. Certain variables were then compared with:

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Gostaria de começar por agradecer à Doutora Carmen Lisboa pela valiosa orientação ao longo de todo o trabalho, demonstrando sempre um forte espírito crítico e científico, e ao Doutor Alberto Freitas pela preciosa ajuda, sobretudo nos aspetos metodológicos e análise estatística, conseguindo sempre responder aos problemas com que me fui deparando.

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Anexos

1. Normas de publicação da Diabetes

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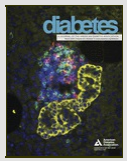

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Please see the corresponding sections below for information on acknowledgments, references, tables, and figures.

Brief Reports

The Brief Report category can be used for any original research pertinent to the journal. The purpose of the category is to permit publication of very important, high-quality mechanistic studies that can be concisely presented. Brief Reports should be formatted in the following manner:

- An **abstract** is required for all Brief Reports. (Please follow the formatting guidelines listed under Original Articles.)
- The **word limit** for the main text of Brief Reports is 2,000 words. (The total word count **excludes** the title page, abstract, acknowledgments, references, tables and figures, and table/figure legends.)
- The report should contain no more than **25 references** and the reference section should be single spaced with justified margins.
- The article should contain no more than a combination of **four tables and/or figures**.
- **Supporting documents/data** can be uploaded for review purposes and will not be published. (When uploading, be sure each file is clearly labeled "supporting document/data.")
- **Online supplemental material** may be uploaded for publishing in an online-only data supplement. Authors must provide a statement of justification as to why it is important for submission and publication if eventually accepted. Only files designated as "Online

Supplemental Data" and approved by the Editorial Committee will be published online.

Please see the corresponding sections below for information on acknowledgments, references, tables, and figures, and online supplemental material.

Review Articles

Diabetes considers two types of review articles: **Methodological Reviews** and **Perspectives in Diabetes**. **Methodological Reviews** provide a comprehensive, critical perspective of research topics and/or methodological approaches that are highly relevant to investigators in the field of diabetes research. It should be interpretative rather than a summary, and should describe various available approaches as well as their relative merits, limitations, and specific applications.
Perspectives may highlight recent exciting research, not primarily that of the author(s), and may provide context for the findings within a field or explain potential interdisciplinary significance (similar to that of a Review Article). Invited Perspectives commenting on papers in Diabetes should add a dimension to the research and not merely be a summary of the experiments presented in the paper. It can also be a critical review that is more interpretational than a summary and, if justified by strong rationale, can propose novel hypotheses.
Reviews are invited or considered for submission based on a proposal from the author(s). Please review the **Instructions for Submitting a Proposal**, and contact Lyn Reynolds (lreynolds@diabetes.org) with any questions.

Commentaries

Commentaries are brief articles presenting the authors' views on a topic of current interest. Commentaries (and Editorials) are by invitation only.

- Commentaries should be limited to 1,000 words, no more one than table and/or figure, and no more than 20 references. For further information regarding Commentaries, please read Commentaries in *Diabetes*, instructions for authors.

Manuscript Submission Tip: To bypass the Abstract field when submitting a Commentary, type None in the Abstract field. For more tips on uploading your manuscript, see the Manuscript Submission Tips section.

Online Letters to the Editor

Online Letters to the Editor are intended to provide an opportunity to comment on articles published within the previous three months in *Diabetes*. Online Letters to the Editor are not intended as a platform for presenting unpublished data, research, or observations.

While Online Letters are only published online, they are listed in the table of contents of the print version, and will be assigned an "E" page number. Citations for Online Letters should include the letter's unique DOI (digital object identifier) number, which is available in the footnote section of each letter (e.g., 10.2337/db08-XXXX).

- Letters do not have abstracts and should not exceed **500 words**, including the references. The inclusion of tables or figures in letters is discouraged. As with all submissions, letters should be double-spaced with 12 pt. Times New Roman font and justified margins.
- Letters must include a **title page** with the authors' full names and affiliations and the corresponding author's contact information.
- For comments on or responses to another article or letter, the article or letter on which the letter comments or responds to should be included as reference 1 in the reference list. The editor reserves the right to ask authors of the cited article to respond.

Manuscript Submission Tip: To bypass the "Abstract" field when submitting a Letter to the Editor, type "None" in the "Abstract" field. For more tips on uploading your manuscript, see the Manuscript Submission Tips section.

Perspectives in Diabetes

Perspectives in Diabetes are invited by the Editorial Board or submitted independently. Perspectives may highlight recent exciting research, not primarily that of the author(s), and may provide context for the findings within a field or explain potential interdisciplinary significance. Perspectives commenting on papers in *Diabetes* should add a dimension to the research and not merely be a summary of the experiments presented in the paper.

The formatting requirements for Perspectives in Diabetes are similar to those for Original Articles.

- An **abstract** is required for Perspectives articles. The abstract should be an unstructured, concise synopsis and may not exceed 200 words. References, primary data, and statistical significance should not be presented in the abstract, and nonstandard abbreviations must be defined.
- The **word limit** for the main text is 4,000 words and 50 references. (The total word count **excludes** the title page, abstract, acknowledgments, references, tables and figures, and table/figure legends.) The main text should be double spaced with justified margins.
- Perspectives may include a combination of no more than eight tables and/or figures.

Please see the corresponding sections below for information on acknowledgments, references, tables, and figures.

Author Contributions paragraph

This paragraph should list each author's contributions as shown on the manuscript submission forms and should be placed in the Acknowledgments.

Acknowledgments

The acknowledgments are located after the main text and before the reference list. Acknowledgments should contain the author contributions paragraph, brief statements of assistance, the guarantor's name (person or persons taking responsibility for the contents of the article), funding/financial support, and reference to prior publication of the study in abstract form, where applicable.

Supplemental Data (Online Supplemental Material)

If you upload **supplemental material** intended for publishing **online-only** it should be labeled as an "Online Supplemental Materials" file. If you upload **supporting data** intended for review purposes only it should be uploaded as "Supporting Data or Supporting Document". Files uploaded as supporting data/supporting document will not be published in print or online if the paper is accepted.

Supplemental data intended as **online-only supplemental material** should contain only supplemental information that is in addition to the main document (additional writing group members/investigator lists, supplemental tables and/or figures, short videos, etc.). It should not be excessively long. Whenever possible, all online supplemental material should be included in one Microsoft Word document file, or otherwise uploaded in its original format.

Note: If you have online-only supplemental material, you must include justification on the necessity of the online supplement. The main document must contain all relevant material. Sections (i.e., Research Design and Methods, Results, Discussion, Conclusions), or portions thereof, cannot be moved to online-only to accommodate word limits in the main document. Each section must be complete, without exception.

References

The reference list should go at the end of the document, after the main text and acknowledgments (if applicable) and before the tables. References should be numbered in the order that they are cited in the text.

Reference numbers in the text should be in normal type and in parentheses [e.g., "In the study by Norton et al. (23)..."]. Please do not use the footnote/endnote functions found in some word processing programs. Reference software is permissible (e.g., EndNotes). Reference lists should be single spaced (no space between citations), and the margins should be justified.

For examples of how to style various citations in the reference list, see "References" in the Manuscript Style section.

Tables

Tables should be double-spaced on separate pages and included at the end of the text document, with the table number and title indicated. Tables should be created using Word and the "Insert Table" command; please do not use tabs and/or spaces to create tables, columns, or rows. Tables with internal divisions (Tables 1*A* and *B*) should be submitted as individual tables, i.e., Tables 1 and 2. Symbols for units should be confined to column headings. Abbreviations should be kept to a minimum and defined in the table legend. Please avoid the use of shading. If a table includes data that require explanation in the legend, apply the following symbol sequence, from top to bottom, left to right: *, †, ‡, §, ||, ¶, #, **, ††, ‡‡, etc.

If tables are taken from other sources, it should be noted in the legend, and the author must be able to provide written permission for reproduction obtained from the original publisher and author.

Figures

Diabetes uses digital publishing methods throughout the journal production process. If your article is accepted, it will be published both in the printed journal and online. The following sections provide information on how to format your figures to ensure the best possible reproduction of your images.

Size. Figures should be produced at the size they are to appear in the printed journal. Please make sure your figures will fit in one or two columns in width. Multi-paneled figures should be assembled in a layout that leaves the least amount of blank space.

1 column = 21 picas wide, 3.5 in, 8.9 cm
2 columns = 43 picas wide, 7.1 in, 18 cm

Font. At 100% size, fonts should be 8-10 points and used consistently throughout all figures.

Text. Information on the axes should be succinct, using abbreviations where possible, and the label on the *y*-axis should read vertically, not horizontally. Key information should be placed in any available white

space **within** the figure; if space is not available, the information should be placed in the legend. In general, figures with multiple parts should be marked A, B, C, etc., with a description of each panel included in the legend rather than on the figure.

Line and bar graphs. Lines in graphs should be bold enough to be easily read after reduction, as should all symbols used in the figure. Data points are best marked with the following symbols, again assuring that they will be readily distinguishable after reduction: ○ ● □ ■ △ ▲. In the figure legend, please use words rather than the symbols; e.g., "black circles = group 1; white squares = group 2; black bars = blood glucose; white bars = C-peptide." Bars should be black or white only, unless more than two datasets are being presented; additional bars should be drawn with clear bold hatch marks or stripes, **not** shades of gray.

Line or bar graphs or flow charts with text should be created in black and white, **not** shades of gray, which are difficult to reproduce in even tones.

Reproductions. If materials (e.g., figures and/or tables) are taken from other sources, it should be noted in the legend, and the author must be able to provide written permission for reproduction obtained from the original publisher and author. For more information, refer to Permissions: Help for Authors.

Figure legends. Figure legends should be clearly numbered and included at the very end of your document and should not be included on the separate figure/image files. Please use words to describe symbols used in the figure; e.g., "black circles = group 1; white squares = group 2; black bars = blood glucose; white bars = C-peptide."

Formatting digital figure files for print and online reproduction. To meet ADA's quality standards for publication, it is important to submit digital art that conforms to the appropriate resolution, size, color mode, and file format. Doing so will help to avoid delays in publication and maximize the quality of images, both online and in print. Please refer to ADA's Digital Art Guidelines when preparing your files. If you are unable to provide files that meet the specifications oulined in the Guidelines, you may submit your origial source files (files from the program in which they were originally created).

The *Diabetes* Editorial Office can properly convert digital figure files as a courtesy for authors who are unable to provide files that meet the specifications. To facilitate this process, please indicate the type of software application(s) used to generate the figure in the form of an e-mail to the Editorial Office (address below) and make sure *original source files* (the initial images created by the original software application) are either uploaded to the submission site or e-mailed to the Editorial Office (diabetesjournal@diabetes.org. If figure files are too large to upload or e-mail, please either upload them on a free web server (http://www.yousendit.com/).

It is strongly recommended that authors converting their own digital files also send the *original source files* (what the figures were created in and saved in that program format) to the *Diabetes* Editorial Office in the event that the converted files are not acceptable for publication for any reason. Unacceptable files include those of poor quality due to improper conversion and/or incorrect resolution (dpi) and/or the use of too many software applications in the creation of the file.

Digital image manipulation. The American Diabetes Association has adopted the statement developed by the *Journal of Cell Biology* as its policy on the manipulation of digital images:

"No specific feature within an image may be enhanced, obscured, moved, removed, or introduced. The grouping of images from different parts of the same gel, or from different gels, fields, or exposures must be made explicit by the arrangement of the figure (i.e., using dividing lines) and in the text of the figure legend. Adjustments of brightness, contrast, or color balance are acceptable if they are applied to the whole image and as long as they do not obscure, eliminate, or misrepresent any information present in the original, including backgrounds. Without any background information, it is not possible to see exactly how much of the original gel is actually shown. Non-linear adjustments (e.g., changes to gamma settings) must be disclosed in the figure legend."

All digital images in manuscripts accepted for publication will be scanned using image forensics software for any indication of improper manipulation. Cases of questionable or inappropriate image alterations will be referred to the Association's Panel on Ethical Scientific Programs (ESP). The ESP may request the original data from the authors for comparison to the prepared figures. If the authors fail to provide the original data, the acceptance of the manuscript will be revoked. Cases of deliberate misrepresentation of data will result in revocation of acceptance, and will be reported to the corresponding author's home institution and/or funding agency as appropriate.

For examples of what constitutes improper digital manipulation (as well as other forms of scientific misconduct), ADA encourages authors to refer to the 2006 editorial by the *Journal of Clinical Investigation* titled "Stop Misbehaving!" In addition, authors are encouraged to refer to Adobe's white paper on using Photoshop CS3 Extended in biomedical imaging. The paper provides useful information on maintaining image integrity, editing nondestructively, and the medical and scientific image workflow.

Manuscript Submission Tip: Figures are to be uploaded individually as separate files. They should be in their original source format (what they were created in) if you are unable to convert figures properly. For more tips, please see the Manuscript Submission Tips section.

Video

Videos can now be published in the online article, with a still image from the video appearing in the PDF and the print version. Still images are encouraged, but not required, and should represent as best as possible the main subject of the video. Video files should be clearly labeled as "video 1," "video 2," etc., and still images should be named "video 1 still image," etc. Each video must be cited in the text, and a legend must accompany each video. Video legends should include labels that correspond with the in-text citation and should be placed after the figure legends in the manuscript.

Videos can also be submitted as supplementary data and should be labeled "online supplemental video 1," etc. Supplementary videos are not required to have legends.

Most video formats are acceptable, including .avi, .flv, .mov, .mp4, .swf, .wav, .wma, .wmv, and more. For helpful information about creating videos, please visit the **Video Creation Guide**.

Cover Art

Authors are invited to submit images for use on the cover of *Diabetes*. Black and white or color photographic or photomicrographic images are acceptable. Examples of recent covers can be found on the *Diabetes* archive page. Cover image submission and selection is completely independent of article submission and the peer-review process. Images sent for consideration on the cover are not required to be

related to an article submitted to or published in the journal. The author must own copyright to the image and, if chosen, must grant ADA unrestricted free use of the image to be published on the cover of the journal as well as in other ADA publications and marketing materials. If your image is selected, you must be able to provide the file in TIFF or EPS format, with a minimum resolution of 300 dpi and no larger than 2MB.

Cover image submissions should be sent to productionmanager@diabetes.org with a brief caption and complete credit information (e.g., photograph courtesy of...). Please limit inquiries regarding the status of your cover image submission. You will be notified in a timely manner if your image has been selected to appear on a cover of Diabetes.

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MANUSCRIPT STYLE

Terminology and Style

Articles should be written in clear, concise English following the recommendations for scientific writing found in *Scientific Style and Format*, the Council of Science Editors (CSE) style manual (7th ed., 2006, Reston, VA, Council of Science Editors). All accepted manuscripts will be edited according to the CSE style manual and *The Chicago Manual of Style* (15th ed., 2003, Chicago, IL, The University of Chicago Press) by ADA professional publications staff. The authors are responsible for all statements made in their articles or editorials, including any editing changes made by staff.

The designations *type 1 diabetes* and *type 2 diabetes* should be used when referring to the two major forms of diabetes. Abbreviations for diabetes, such as *T2D* for *type 2 diabetes*, should not be used. The term *diabetic* should not be used as a noun.

Abbreviations

Abbreviations should be used only when necessary, e.g., for long chemical names (HEPES), procedures (ELISA), or terms used throughout the article. See the list of abbreviations that need not be defined; all others must be defined at first use. Abbreviate units of measure only when used with numbers. Abbreviations may be used in tables and figures. The CSE style manual contains lists of standard scientific abbreviations.

Units

Clinical laboratory values should be in Système International (SI) form. Kilocalories should be used rather than kilojoules. HbA1c values should be dually reported as "% (mmol/mol)." Please use the NGSP's HbA1c converter at http://www.ngsp.org/convert1.asp to calculate HbA1c values as both % and mmol/mol.

Materials

Authors should provide the name and location (city and state/country) of the source for specified chemicals and other materials only if alternate sources are considered unsatisfactory.

References

References should be listed according to the following examples and should be numbered in the order that

they are cited in the text. All authors must be listed and inclusive page numbers provided. Journal titles should be abbreviated as in the National Library of Medicine's List of Journals Indexed for Medline; for unlisted journals, complete journal titles should be provided. Material that is in press may be cited, but copies of such material may be requested. Authors are responsible for the accuracy of the references.

When citing the **prepublished version** of a *Diabetes* article, please use the DOI (digital object identifier) in place of volume, page range, and year (see below for an example). The DOI of a *Diabetes* article will begin with 10.2337, followed by an article number (assigned at submission via the online manuscript submission system) (e.g., 10.2337/db08-XXXX).

> Example: Kohler C, Norton N, Farber K, Briggs E: How to cite a prepublished article in ADA journals. *Diabetes* 10.2337/db08-9999

Scientific Sessions **abstracts** from 2003 to present can be found using the link provided at the bottom of the *Diabetes* archive page (http://diabetes.diabetesjournals.org/contents-by-date.0.shtml).

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MANUSCRIPT SUBMISSION TIPS

- Your manuscript should be submitted under the name of the designated **corresponding author's user account** (the contact person listed on the title page of the manuscript); the corresponding author is the only author who will receive notification of proof availability. (The system automatically recognizes the user account as the corresponding author, even if another name is designated.)
- Be sure to **review the proofs** of your submitted files after uploading them.
- To bypass the **"Abstract" field** when submitting a Letter to the Editor or a Commentary, type "None" in the "Abstract" field, and when submitting a Perspectives, paste the introduction into the "Abstract" field.
- Use simple **file names** when saving your documents, and do not use special characters such as [brackets], (parentheses), punctuation marks (?, !, .), or symbols (@, #, &, etc.). In addition, avoid spaces in files names, e.g., use "Figure1.tif" rather than "Figure 1.tiff."
- Do not upload .pdf files, Excel files, or zipped files (unless you are uploading original source files of figures). You may, however, upload .pdf copies of the signed **manuscript submission form**, which can be found in the Editorial Policies section and must be provided for all manuscript submissions.
- The text of your manuscript should be prepared using a word processing program and saved as a .doc, .txt, or a .rtf file.
- When uploading each file, you will be asked to choose a designation from a pull-down menu that describes the content of the file (e.g., "Main Document," "Figure," "Table," etc.). In addition to this designation, please ensure that the name of each file clearly describes the content of the file (e.g., "figure1.tiff," "table2.doc," "coverletter.rtf," etc.).

Revisions

In addition to following the above listed guidelines for submission:

- When submitting a revised manuscript, all changes should be indicated with red font and underlined. Deletions need not be indicated within the article itself but should be noted in the author responses to reviewers.
- If the "track changes" function of a word processing program is used to show additions and deletions, make sure that all changes are "accepted" before submitting the clean revised version. Once the changes are accepted, deactivate the track changes function before saving

and uploading the file.
- Please provide both a marked version showing corrections and a "clean" final version.
- Do not "lock" or "page protect" documents.
- Please adhere to word count, table, and figure limits as previously instructed.

Failure to follow instructions may result in publication delays if your manuscript is accepted.

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ACCEPTED MANUSCRIPTS

Accepted manuscripts will be scheduled for publication as soon as possible.

Correspondence concerning the copyediting and proofreading of accepted manuscripts should be addressed to Nancy Baldino, Editorial Manager, *Diabetes*, American Diabetes Association, 1701 North Beauregard St., Alexandria, VA 22311; tel.: (703) 253-4367; fax: (703) 253-4870; e-mail: nbaldino@diabetes.org.

Correspondence concerning the production of accepted articles should be addressed to Amy Gavin, Production Editor, American Diabetes Association, 1701 North Beauregard St., Alexandria, VA 22311; e-mail: agavin@diabetes.org.

The designated corresponding author will receive notification of availability of page proofs by e-mail. Corrections should be returned within 24 hours of receipt of the proof. Failure to do so may delay the publication of the article to another issue. If an extension is required, please contact either Nancy or Amy at the addresses/phone numbers above.

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FINANCIAL OBLIGATIONS

Page charges are assessed for Original Articles and Brief Reports to help defray costs of publication. The charge is $90 per page. In addition, each color figure printed will incur a charge of $460. (Note: Charges apply to each figure as a whole, not by the part, i.e., *A*, *B*, *C*, etc.). The corresponding author will receive via e-mail an invoice, as well as a reprint order form, when page proofs become available. Unless otherwise indicated, the corresponding author is to assume responsibility for payment.

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