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Hospitalization for Charcot neuroarthropathy in diabetes: A population study in Italy

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ABSTRACT

Aims: To provide data on hospitalization and incidence rates of Charcot neuroarthropathy (CN) and its relation to lower limbs' amputations/revascularizations in population with diabetes of Italy as well as of one of its regions (Tuscany).

Methods: Hospitalizations with CN diagnosis (codes ICD-9-CM: 7130, 7135, 7138) have been recorded in people with diabetes over years 2003–2013 in Italy and 2008–2015 in Tuscany. Amputations, peripheral vascular disease, revascularizations and infections were likewise evaluated.

Results: Between 2003 and 2013 CN hospitalizations were very infrequent in Italy ranging between $14 \times 100,000$ and $11 \times 100,000$ patients with diabetes. In Tuscany they declined to a minimum of $7 \times 100,000$ patients in 2015, after a previous increase to a maximum of $22 \times 100,000$ ($p = \text{NS}$ for both). Yearly CN incidence remained constant in Italy, declining in Tuscany to a minimum of $3.4 \times 100,000$ diabetic patients in 2015 ($p = 0.047$). CN patients were younger and with longer length of hospital stay than those with non-Charcot diabetic foot ($p < 0.05$ for both). Amputation and infection rates were manifold higher in CN patients than in those with non-Charcot diabetic foot, while the revascularization rate was similar in both. **Conclusions:** Over last decade, in Italy and Tuscany yearly CN incidence and hospitalization rates concerned only a small percentage of patients, remaining constant over years and declining in Tuscany in the last couple of years. CN was significantly associated to younger age, longer hospital stay and greater risk of amputations and infections while the need of revascularization was similar to that of non-Charcot diabetic foot.

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1. Introduction

Charcot neuroarthropathy (CN) represents a distinct entity within the clinical frame of diabetic foot [1–6]. CN is charac-

terized by an inflammatory syndrome, associated with varying degrees of foot disease mainly caused by diabetic neuropathy [2,4,6], which progressively leads to a deep derangement in both anatomy and function of feet and

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related joints. All this leads to disruption in quality of life of patients with diabetes and, ultimately, to the eventuality of both major or minor amputations of lower limbs especially if complicated by ulcers [7], even if previous studies have demonstrated a similar or even lower incidence of peripheral artery disease in these patients [8].

Furthermore, CN diagnosis is often missed or elusive being a common belief that it is a rare complication of diabetes [4] and, as a matter of fact, its prevalence has not yet clearly been determined, largely ranging, according to previous reports, from less than 1 to about 100 of 1000 patients with diabetes in different populations [3,9–11]. A further reason of this heterogeneity in estimates may be due to the fact that most studies concerned small populations whose recruitment was often characterized by scarcely defined selection criteria.

For these reasons we performed a study investigating hospitalization rates due to CN in Italy. Since no national registries of patients with diabetes do exist in Italy, the only way to evaluate CN prevalence was indeed to identify hospitalization rates with CN diagnosis. We had moreover the opportunity of querying a dataset concerning a well defined diabetic population living in Tuscany, a region of central Italy, and thus of comparing Italian and Tuscan data regard to CN hospitalization rates.

2. Materials and methods

2.1. Data source

This study concerned two populations with diabetes: (i) the whole Italian population followed up in the period 2003–2013 and: (ii) the population of Tuscany, Italy over years 2008–2015.

2.2. Italian population

For this population data were extracted from the National Hospital Discharge Record database held by the Italian Ministry of Health (<http://www.archeo.salute.gov.it/ricoveriOspedalieri/ricoveriOspedalieri.jsp>) and elaborated at the National Centre for Epidemiology, Surveillance and Health Promotion, National Institute of Health (Istituto Superiore Sanità), Rome, Italy. This database contains administrative data regarding all yearly admissions to public and private hospitals in Italy, including day-hospital (less than 24-h of stay). Information available from this database and used in the present study was: hospital code, individual patient code, age, sex, region of residence, citizenship, admission and discharge dates, discharge status (i.e. ordinary, voluntary discharge, or transferred to other hospital, dead), main discharge diagnosis and up to five additional diagnoses, Diagnosis Related Group (DRG) code, main procedure as well as up to five further procedures. Diagnoses and procedures were coded using the International Classification of Diseases-Clinical Modification, 9th edition (ICD9-CM). Data provided by the Ministry of Health are anonymous but the individual code allows for the record linkage on the same patient over different years.

For this study we utilized all hospital discharge records, from January 1st 2003 to December 31st 2013, with referenced

ICD9-CM code of CN: 7130, 7135, 7138 [7,12,13] in both primary or secondary diagnosis as well as with diagnosis of diabetes (250.x) recorded in the same hospital discharge or in any discharge during the same year. In addition procedures of both major or minor lower extremity amputations (ICD9-CM codes 8410–8419), or revascularizations (surgical: ICD9-CM codes 3925, 3929, endoluminal: ICD9-CM codes 3950, 3990) as primary or secondary were identified. For each Italian region the population with diabetes was obtained from ISTAT (National Institute of Statistics) (<http://www.istat.it/it/>). The resulting final database consisted of 4416 hospitalizations concerning CN in both primary or secondary diagnosis. The yearly rates of hospitalizations and, consensually, of patients who were admitted to hospital for the first time with diagnosis of CN incidence rates were then counted and expressed as No. x1000 or x100,000 people with diabetes.

2.3. Tuscan population

For the analysis of the population of Tuscany- a region of central Italy with 3,744,398 living inhabitants according to 2015 census [14] the database was based on all hospital discharges over years 2008–2015 from all Tuscan hospitals. In this region public hospitals cover more than 90% of total hospital admissions. The survey began in 2008 because the population was identified by the regional registry of diabetes, previously used for similar studies and fully active and consolidated since 2008 [15]. This database is estimated to cover more than 80% of all diabetic patients living in Tuscany [15], giving a total number of 264,221 individuals with diabetes in year 2015, which represents the 7.05% of total population. Diagnosis of CN as well as that of lower limbs' amputations or revascularization have been done by using the same ICD9 codes utilized for the whole Italian population. Diagnosis of non-Charcot diabetic foot was done in case of ICD9 codes 707.13, 707.14, 707.15 (diabetic foot ulcers) or of amputations' procedures (major: 84.15, 84.16, 84.17, 84.18 or minor: 84.11, 84.12) or revascularizations (both surgical or endoluminal: (3925, 3929, 3950, 3990) in either primary or secondary diagnosis in absence of CN diagnosis codes. Amputations were coded as minor in over the 80% of cases, either in those with or without CN. Revascularizations were endoluminal in over the 90% of cases. In addition patients with diabetic foot were stratified by co-presence of infections or of peripheral vascular diseases according to ICD9 codes as summarized in Table 1 [16].

After querying the dataset a total of 19,456 hospitalizations have been recorded pertaining to 10,169 individuals with diabetes. Also in this case yearly rates of both hospitalizations and of patients admitted to hospital for the first time were counted and expressed as No. x1000 for amputations and revascularization rates or x100,000 people for rates of CN.

Neither ethical approval nor individual written consent by patients was requested as the data were retrospective and anonymous.

2.4. Statistical analysis

Prevalence rates were computed for each year, and the time trend of events was calculated by Kendall Tau correlation analysis, evaluating annual rates over the entire observation's

Table 1 – Yearly hospitalization and prevalence rates ($\times 100,000$ subjects with diabetes), mean length of stay in hospital (LOS) and sex of diabetic patients with Charcot neuroarthropathy (CN) in Italian and Tuscan population over years 2003–2013 and 2008–2015 respectively. In bold: data concerning the overlapping period.

Year	Italian population (No. 4416)						Tuscan population (No. 323)					
	Hosp. No.	Patient No.	Sex (% M)	LOS days	CN hosp. rate ($\times 100,000$ patients with diabetes)	CN incidence rate ($\times 100,000$ with diabetes)	Hosp. No.	Patient No.	Sex (%M)	LOS days	CN hosp. rate ($\times 100,000$ patients with diabetes)	CN prevalence rate ($\times 100,000$ with diabetes)
2003	365	314	60	10	16.3	14						
2004	337	285	62	11	14.4	12						
2005	348	297	58	13	14.3	12						
2006	370	310	63	13	14.2	12						
2007	384	317	62	12	14.1	12						
2008	391	317	61	12	13.7	11	29	23	72	10	15	11.9
2009	413	355	67	12	14.3	12	37	26	78	12	17.8	12.5
2010	455	365	67	12	15.4	12	46	26	63	12	20.3	11.5
2011	475	391	68	12	16.2	13	51	31	72	10	21.4	13
2012	460	382	66	11	13.9	12	56	30	75	12	22.5	12.1
2013	418	345	61	12	12.7	11	49	25	75	9	19.2	9.8
2014							36	25	55	11	13.8	9.6
2015							19	9	68	11	7.2	3.4

Table 2 – Hospitalization rates associated with lower limbs' amputations or revascularizations over years 2008–2015 in patients hospitalized for Charcot neuroarthropathy, as compared with non-Charcot diabetic foot in Tuscan population.

	Tuscan population		
	Non-Charcot diabetic foot	Charcot neuroarthropathy	Charcot neuroarthropathy without ulcers ^{**}
	No. (hospitalization rate in patients with diabetic foot in years 2008–2015)	No. (hospitalization rate in patients with Charcot in years 2008–2015)	No. (hospitalization rate in patients with Charcot in years 2008–2015)
Peripheral vasc. disease (PVD)	1531/5417 (28.2%) [*]	35/323 (11%)	33/245 (13%)
Infections	316/5417 (5.8%)	84/323 (26%)	73/245 (30%)
Both infections and PVD	1791/5417 (33%)	104/323 (32%)	91/245 (37%)
Amputations	202/5417 (3.7%)	52/323 (16%)	47/245 (19%)
Revascularizations	660/5417 (12.2%)	37/323 (11.4%)	32/245 (13%)

^{*} $p < 0.0001$ after Chi-square, comparing prevalence of amputations of CN subjects with those with non-Charcot diabetic foot.

^{**} Charcot codes without ICD9 codes 70.713, 70.714, 70.715 (foot ulcers).

period. All analyses were performed using STATA Ver. 12 (College Station, TX, USA), or with SAS software, ver. 9.3 (SAS Institute, Cary, NC, USA).

3. Results

In the Italian population we observed a total of 4416 hospitalizations corresponding to 3678 patients who were admitted to hospital with primary or secondary diagnosis of CN over the period 2003–2013. In Tuscany, a total of 323 hospitalizations were counted corresponding to 195 patients with CN diagnosis who were discharged by hospital at least once over years 2008–2015. Of these 323 hospitalizations the diagnosis was not associated with ICD9-CM codes 70.713, 70.714, 70.715 (foot ulcers) in 245 cases (77%). Repeated admissions were evident in Italy and Tuscany counting percentages of 20 and 65% respectively. In Tuscan population, the rate of patients discharged with diagnosis of non-Charcot diabetic foot totalled 5339 hospitalizations and 2631 patients.

In Tuscan population the mean age of patients with CN was 60 ± 13 yr, significantly lower than in those discharged with diagnosis of diabetic foot: 73 ± 11 yr; $p < 0.0001$.

Table 2 reports the total number of patients discharged with CN diagnosis in Italian and in Tuscan populations over the respective study periods. In the overlapping period (2008–2013) the hospitalization rate, starting from similar values in year 2008 then became higher in Tuscan than in Italian population growing up much more in Tuscany until year 2012 and then dropping over the last years in both cohorts. Patients with non-Charcot diabetic foot showed similar

trends in both populations (data not shown). Male sex was much more prevalent in patients with CN diagnosis and length of stay in hospital (LOS) was on average equal or longer than ten days in both Italian and Tuscan population and was significantly longer than in those with no-Charcot foot diagnosis (11 ± 4 days vs. 7 ± 3 days; $p < 0.0001$). CN hospitalization showed a wide variability among Italian regions in year 2013, spanning from a rate of $4.5 \times 100,000$ subjects with diabetes of Sardinia to a maximum of $26.8 \times 100,000$ of Molise, with a variation coefficient equal to 52.6% (Suppl. Table).

The rates of hospitalizations for lower limbs' amputations (mostly minor), total revascularizations (mostly endoluminal), and the prevalence rates of hospitalizations of patients in Italian or Tuscan population are graphically represented in Fig. 1. Hospitalization rates for amputation were on average lower while rates for revascularization were higher in Tuscany. In addition, amputation rates were significantly decreasing either in Italy and Tuscany over the last years with a rate ranging from 3.6 to 2.7×1000 persons with diabetes in period 2003–2013 in Italian population and from 2.6 to 1.9×1000 persons with diabetes in period 2008–2015 in Tuscany ($p < 0.01$ for both after trend analysis). The rate of revascularizations (most of which were endoluminal) remained constant in Italian cohort ranging from 4.0 to 4.8×1000 persons with diabetes in period 2003–2013 ($p > 0.05$) and decreased from 7.1 to 5.4×1000 persons with diabetes in period 2008–2015 in Tuscany ($p < 0.01$) after trend analysis. CN hospitalization rate was similar in year 2008 and then was much higher in Tuscan than in Italian population increasing much more in Tuscany until year 2012 and then dropping over

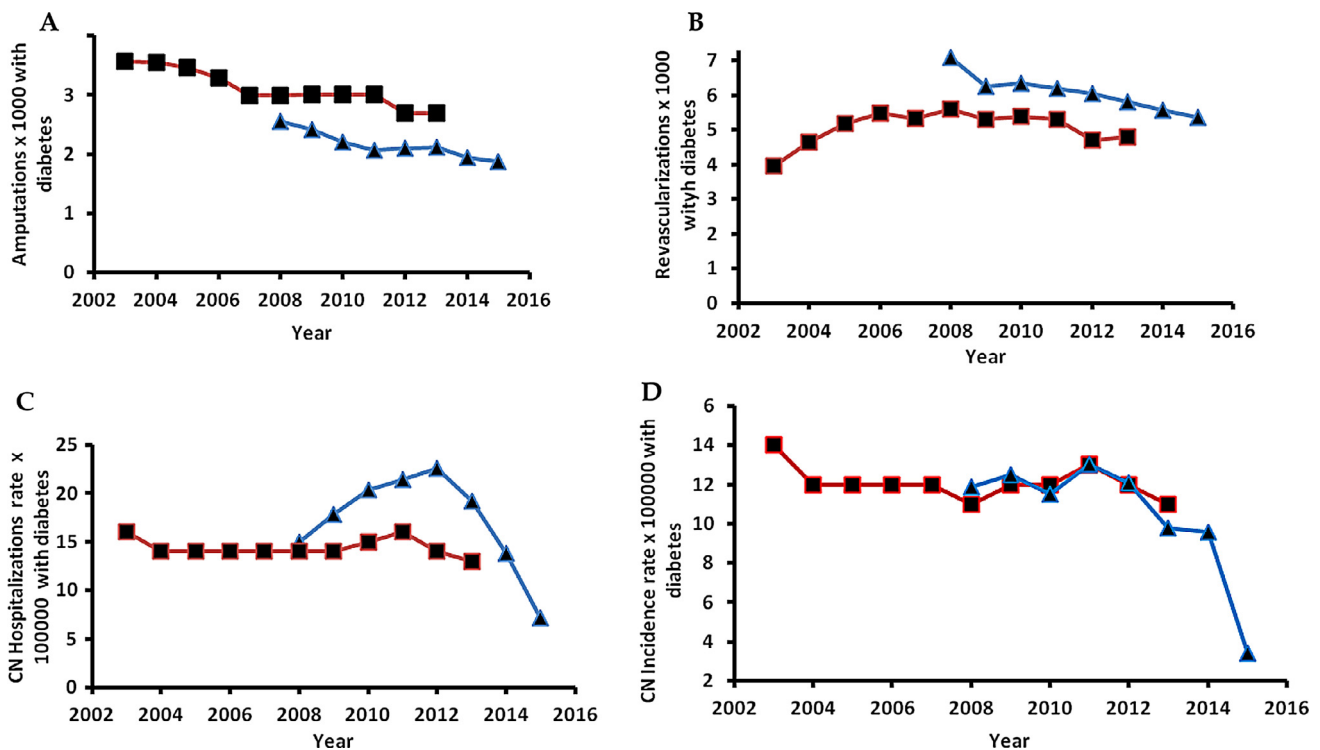


Fig. 1 – Rates of hospitalizations for lower limbs' amputations (A), or revascularizations (B) and hospitalization and incidence rate for Charcot neuroarthropathy (C and D) in Italian (■) or Tuscan population (▲) over years 2003–2013 and 2008–2015 respectively.

last years in both populations ($p > 0.05$ after trend analysis for both). Yearly CN incidence remained constant in Italy, declining, even if marginally, in Tuscany to a minimum of $3.4 \times 100,000$ diabetic patients in 2015 ($p = 0.047$, after trend analysis in this latter; Fig. 1, D), and the discrepancy between the incidence rate of patients admitted to hospital for the first time and that of hospitalizations, similar in Italy and in Tuscany, seems to be mainly due to the higher number of repeated hospitalizations in this latter (20% vs. 65%).

Patients with diagnosis of CN had moreover a fourfold higher hospitalization rate for amputations compared to those who received a diagnosis of non-Charcot diabetic foot ($p < 0.0001$; after Chi-square test), while the revascularization rate was similar in both cases (Table 2). Interestingly, the rate of peripheral vascular diseases was significantly higher in patients without CN codes while, on the opposite, the infection rate was significantly more prevalent in patients hospitalized for CN, even more evidently when considering the 245 hospitalizations without diabetic foot ulcers (codes 70.713, 70.714, 70.715) more seemingly assimilated to CN, in complete agreement with Wukich et al. [8] (Table 2).

4. Discussion

Charcot described about one-and-half centuries ago a peculiar neuroarthropathic condition affecting feet [17], only later associated with diabetes [18]. However, even if a long time has elapsed from the initial description, the real burden of CN in diabetes has not been clearly well defined, spanning in previous studies from a rate of 0.08 to a rate as high as 29% [3,9–11]. This can be firstly due to the fact that previous studies have been mostly performed in selected groups of patients often containing a reduced number of individuals. Some studies used, in fact, clinical databases inevitably including a limited number of well selected patients, while others, regarding larger populations used, as in our case, hospital discharge databases: and this discrepancy can produce different evaluations in the incidence rate of CN, even in a same population. A further hindrance to a more precise definition of the real CN prevalence is possibly linked to its racial or geographic variability [10,13,19–22] as also suggested by the great variability in prevalence rates among Italian regions. This may be due to a different attitude to code CN although a real epidemiological difference among regions cannot be excluded. This is a further reason that prompted us to design this study which introduces Italian data, comparing them with those obtained from a more homogeneous setting as in Tuscany.

Furthermore, to the best of our knowledge, the present report is the first population study inquiring about the CN hospitalization rate in diabetes in Italy. This study has moreover been performed comparing two different geographical epidemiological realities i.e. Italy as a whole and one of its regions Tuscany. Mean rates of CN patients either from Italian or Tuscan population are very small ranging between about 0.003 and 0.014%, thus manifold lower when compared to those previously reported by literature. In the TRIAD study, for instance, which used administrative data to identify CN, and therefore methodologically very similar to ours, CN prevalence was higher (0.78×1000 patients with diabetes), interestingly mirroring a much greater amputation rate (15.4×1000 patients

with diabetes) than in our case [23]. We can thus conclude that CN hospitalizations seem to be marginal in our country as well as in Tuscany consisting in about the 6% of total hospitalizations for diabetic foot. Interestingly, the low CN hospitalization rates we have observed parallels the low risk of amputations or of total hospitalizations for diabetic foot observed in Italy compared with some other countries [24], and could testify a more careful local adherence to established guidelines aimed at the prevention of foot lesions in patients with diabetes [25]. However, a possible CN underestimation cannot be excluded since the clinical entity referring to CN could have been not entirely captured by used specific ICD-9 codes, due to the only administrative source of the data.

Mean age of patients with CN in our study was very similar to that reported by a recent epidemiological study [11,26] and associated with a younger age than what observed in those with non-Charcot diabetic foot, suggesting a different natural history for these two conditions.

Rate of hospitalized patients with CN in diabetes remained quite constant in Italian population, while in Tuscany it rose in period 2008–2012 and then dropped until 2015, due to the fact that repeated hospitalizations were, at least initially, more frequent in Tuscan than in Italian population, as also suggested by the reduction trend in CN incidence rate observed in Tuscany during the period 2008–2015 ($p = 0.047$ after test for trend). However the comparison between the time-courses in the two populations may present inaccuracies, due to the fact that the population of patients with diabetes (denominator) is differently computed in the two cases, presumably with a greater accountability for numerators (number of cases).

Hospitalizations with CN diagnosis were linked with an about fourfold greater risk of amputations, compared to those with non-Charcot diabetic foot diagnosis. This finding is moreover reinforced by the observation that the higher amputations' prevalence is present also in to the group of 245 hospitalizations without ulcers and thus with a more proper CN diagnosis. Studies reporting long term trends indicate that amputations' rate is declining over past years in western countries as well as in Italy [27], as also confirmed by the present study, mostly concerning minor amputations. A similar trend was observed for revascularizations, statistically declining only in Tuscany, which was on the contrary associated with a higher mean rate, compared to the Italian rate (Fig. 1B). The higher prevalence of amputations (mostly minor) in CN is in agreement with previous observations [6,28,29] and in disagreement with others [8]. Our data suggest moreover suggest a tight relationship between infections and amputations in diabetic patients with CN. While, in fact, the rate of peripheral vascular diseases is significantly lower and the prevalence of those with both infections and peripheral vascular diseases is similar in patients with CN as compared to those with non-Charcot diabetic foot (see Table 2), the infections are significantly more prevalent in subjects with CN, either with or without foot ulcers. As a consequence of this the more probable cause of amputations (mainly minor) in CN seems to be due to infectious complications, more than to peripheral vascular complications. This does not exclude the possibility of a greater risk of worse or more complex prognosis, in terms of reduced limbs or foot rescue,

in patients with both CN and peripheral vascular disease [30,31]. Even in absence of previous certain data, however, it is of interest to report the lack of any increase in revascularization rate, which remained similar to that observed in non-Charcot diabetic foot. Again all this recalls the complex pathogenetic entity of CN, endowed with a greater risk of local infections, neuropathic damage or both, more than with a mere vascular pathogenesis [4].

Finally a further feature of CN is the longer length of hospitalization stay, as compared with non Charcot diabetic foot either in both Italian and Tuscan population, in agreement with a recent report from an US study [32]. Interestingly, according to this latter the longer stay in hospital was mainly due to foot infections and was associated with greater costs and higher inpatient mortality.

4.1. Limitations and strengths of the study

This study has a main limitation: it is based on administrative data which do not allow considering important clinical variables useful to validate the diagnosis of CN and to better characterize these patients. A further limitation is that our method included only hospitalized patients, presumably the more complicated ones, not considering those who were followed up as outpatients. Even if this is a major limitation, there to remember however that CN identification by hospital discharges utilizes ICD-9 codes that are well referenced for epidemiological purposes [16]. Our study has the major strength of being a wide population study evaluating large populations, covering both a nationwide and a regional hospitalization series of patients with diabetes discharged from hospital with CN diagnosis.

4.2. Conclusions

In conclusion this study, which considers diabetic populations living in Italy and respectively in Tuscany, suggests that, over last decade, CN concerns a very small percentage of hospitalizations and its rate remains constant, falling in Tuscany, after a previous relative increase. Likewise, yearly CN incidence rates show similar trends significantly declining in Tuscany to a minimum of $3.4 \times 100,000$ diabetic patients in 2015. In addition, patients with CN diagnosis seem to be younger than those with non-Charcot diabetic foot and have a longer length of stay during hospitalizations. Finally, in patients with CN there is evidence of a significant association between the rate of hospitalizations and that of amputations and of infections, even in front of a lower prevalence of vascular complications, while the prevalence of revascularizations seems to be similar to that of non-Charcot diabetic foot. All this confirms that CN is a different clinical entity, compared to non Charcot diabetic foot, being, moreover, a serious and potentially limb-threatening complication of diabetes.

Conflict of interest

The authors declare that they have no conflict of interest.

Authors' contribution

R.A., F.L., M.M., P.F. and A.D.B. conceived and designed the study; L.P., F.L., M.M. and G.S. analyzed the data; G.S. and R.A. wrote the paper; E.B., E.S, A.T. and S.V. discussed and edited the manuscript. G.S. and R.A. are moreover the guarantors of this paper, had full access to all the data in the study and take the responsibility for the integrity of data and accuracy of data analysis.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabres.2017.03.029>.

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