Hidden kidney damage in diabetic patients: A single-center observational study.

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Abstract

Introduction: Up to 40% of patients with type 2 Diabetes mellitus (T2DM) develop diabetic nephropathy (DN). This variable proportion depends on several intrinsic factors of the population. The study’s objective was to describe the renal functional stage of patients with T2DM and to demonstrate the incidence of occult kidney damage in patients admitted to a provincial reference center for patients with T2DM in Holguín, Cuba.

Methods: The present observational, cross-sectional, and prospective study was conducted at the Provincial Diabetic Center in Holguín from March 2019 to March 2021. Cases of patients with T2DM were included. The variables were demographic and clinical (Albuminuria, hyperglycemia, hypertension, proteinuria, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, and fundus). The sample was probabilistic of 377 cases. Descriptive statistics are used.

Results: 537 patients with T2DM were analyzed, including 341 women (63.5%). Patients > 60 years old were 259 (48.2%). The time of diagnosis of T2DM was <1 year in 270 cases (50.3%). 74 cases (13.8%) were patients with already established DN. Patients with obesity and overweight were 74.9%. The presence of albuminuria in grades A2 and A3 was 21.2% (CI95 17.8-24.7%). 60% of cases presented hypertriglyceridemia. High blood pressure occurred in 75.6%. In 79 cases (14.7%), there was diabetic retinopathy. CKD-EPI stage 2 were 254 cases, 47.3%.

Conclusion: Most patients with T2DM (82.1%) have chronic kidney disease in stages 2 to 5. Over half (60%) present hypertriglyceridemia, obesity, and high blood pressure.

Keywords:
MeSH: Diabetes Mellitus, Type 2; Observational Study; Renal Insufficiency, Chronic; Nephrology; Proteinuria.

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Type-2 diabetes mellitus (T2DM) is characterized by varying degrees of insulin resistance, decreased secretion, and increased glucose production. The risk of chronic complications increases depending on the duration and intensity of hyperglycemia, and one of the leading causes of morbidity and mortality secondary to this is the associated kidney disease [1].

Twenty-five to 40% of patients with diabetes mellitus develop diabetic nephropathy [2, 3]. One of the best predictors of kidney damage is albuminuria [4]. The most accepted method for screening for microalbuminuria is the urinary albumin/creatinine ratio. However, there is a group of patients who, in the absence of albuminuria, have normal apparent serum creatinine, with a measurement of the glomerular filtration rate (GFR) <60 ml/min/1.73 m, which has been called occult kidney disease [5]. The diagnosis is based on establishing chronic reduction in kidney function and structural kidney damage. Therefore, to determine kidney damage, damage markers such as the assessment of urinary albumin expressed as microalbuminuria must be used [6].

There are various parameters to determine the presence of microalbuminuria, such as albumin excretion rate in 24-hour urine, albumin/creatinine ratio in a random urine sample, and albumin concentration in the first-morning urine [6].

The best indicator of kidney function is the measurement of glomerular filtration rate, which is equivalent to the amount of fluid filtered by functioning nephrons per unit of time. Therefore, to evaluate the glomerular filtration rate, serum creatinine and urinary creatinine must be determined in 24-hour urine. Serum creatinine is determined using a specific test with adequate traceability to international reference standards and with minimal deviation from the reference method of isotopic dilution mass spectrometry [7].

Several equations use standardized creatinine methods and allow the estimated glomerular filtration rate to be calculated; however, the measurement is more accurate than the estimate since current formulas overestimate the glomerular filtration rate, and possible early cases of diabetic nephropathy may go unnoticed. Within the glomerular filtration rate prediction equations, the CKD-EPI equation (Chronic Kidney Disease-Epidemiology Collaboration) provides greater accuracy and improves the predictive capacity of glomerular filtration rate, the prediction of mortality (overall and cardiovascular) and the risk of developing end-stage chronic kidney disease; therefore, the estimated glomerular filtration rate is recommended for calculation [7].

The objective of the present study was to determine the incidence of occult kidney damage in patients admitted to a provincial center for diabetic patients in Holguín, Cuba.

Materials and methods

Study design
The study is a cross-sectional descriptive observational study. The source is prospective.

Scenery
The study was carried out in the primary health care service at the Provincial Diabetic Center in Holguín, Cuba. The study period was from March 1, 2019, to March 31, 2021.

Participants
Cases of patients over 17 years of age who were consulted for the presence of type 2 diabetes mellitus were included. Previously confirmed cases of diabetic nephropathy were excluded. Cases with incomplete records were eliminated from the analysis.

Variables
The variables studied were as follows:
- **Demographics**: age, sex, weight, height, body mass index, and abdominal circumference.
- **Clinical**: Urinary albumin in 24 hours, hyperglycemia (>7.0 mmol/l), hypertension (>130/80 mmHg), proteinuria in 24 hours, hypercholesterolemia (>6.5 mmol/l), hypertriglyceridemia (>1.8 mmol/l), hyperuricemia (>412 mmol/l), fundus.
- **Habits**: smoking.

Data sources/measurements
The source was direct. The information was collected in an electronic database created by the authors from patient surveys. Biochemical measurements, biopsies, and treatments were part of the institution's regular activity. They are routinely carried out in diagnostic and control studies collected from the institution's laboratory system.

Biases
To avoid possible interviewer, information, and memory biases, the primary researcher always kept the data with a guide and records approved in the research protocol. Observation and selection bias were avoided with the application of participant selection criteria. All clinical and paraclinical variables from the period already mentioned were recorded. Two researchers independently analyzed each record in duplicate, and the variables were recorded in the database once their agreement was verified.

Study size
The population comprised patients with type 2 diabetes mellitus in Holguín. In Cuba, according to a study published by the University of Medical Sciences of Havana, the prevalence of type 2 diabetes was 6.67% in 2019 [8]. For the population of Holguín of 294,965 inhabitants, an unadjusted rate of 19,674 cases corresponds to a universe. With a confidence level of 95%, an expected frequency of 50%, and a confidence limit of 5%, the sample size was 377 cases. Epi Info™ Version 7.0 was used. (CDC. Atlanta, GA: Centers for Disease Control and Prevention, 2023) for sample calculation.
Quantitative variables
Descriptive statistics were used. The results were expressed on a scale of means and standard deviation. Categorical data are presented in proportions.

Statistical analysis
Descriptive statistics are used. Relevant prevalence results are presented with a 95% confidence interval for a proportion. The statistical package used was SPSS 20.0 (IBM Corp. Released 2011. IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.).

Results
Study participants:
A total of 537 patients entered the study.

Description of the general characteristics of the group
There were 196 men (36.5%) and 341 women (63.5%). The highest percentage corresponded to patients over 60, with 259 cases (48.2%). The time of diagnosis and treatment of type 2 diabetes in most of the groups was less than one year (Table 1).

Clinical characteristics of the study population
Seventy-four cases (13.8%) were patients with chronic kidney disease with serum creatinine elevations above the expected value. Among patients who were obese and overweight, they constituted 74.9% of the cases. White patients accounted for 75.8% of the cases.

Table 1. Distribution of patients admitted to the study.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Male sex</th>
<th>Female sex</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Under 40</td>
<td>15</td>
<td>2.8</td>
<td>16</td>
</tr>
<tr>
<td>41 to 59</td>
<td>91</td>
<td>17.0</td>
<td>156</td>
</tr>
<tr>
<td>Over 60</td>
<td>90</td>
<td>16.7</td>
<td>169</td>
</tr>
<tr>
<td>Total</td>
<td>196</td>
<td>36.5</td>
<td>341</td>
</tr>
</tbody>
</table>

Diagnosis time of type 2 Diabetes Mellitus.

<table>
<thead>
<tr>
<th>Diagnosis time of type 2 Diabetes Mellitus</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 year</td>
<td>270</td>
<td>50.3</td>
</tr>
<tr>
<td>1 to 5 years</td>
<td>91</td>
<td>16.9</td>
</tr>
<tr>
<td>11 to 15 years</td>
<td>66</td>
<td>12.3</td>
</tr>
<tr>
<td>16 to 20 years</td>
<td>59</td>
<td>11.0</td>
</tr>
<tr>
<td>&gt;20 years</td>
<td>22</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Grade A2 and A3 albuminuria was present in 21.2% (CI95 17.8-24.7%) of patients. Regarding the risk factors (Table 2), 60% of the cases had hypertriglyceridemia, and 57% had an abdominal circumference > 90 cm in women and > 100 cm in men. High blood pressure was the most frequently associated chronic disease (75.6%) (Table 2).

Target organ involvement
In 79 cases (14.7%), there were renal parenchymal lesions with increased echogenicity, which determined the presence of chronic alterations accompanying diabetic nephropathy. In 79 cases (14.7%), there were also lesions associated with diabetic retinopathy in the fundus (Table 3). The presence of nephrolithiasis was incidental in 63 cases (11.7%), as was the presence of simple renal cysts in 38 cases (7.1%).

Table 2. Clinical characteristics of the patients entered into the study.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Classification</th>
<th>Total</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine</td>
<td>Normal</td>
<td>463</td>
<td>86.2</td>
</tr>
<tr>
<td></td>
<td>Elevated</td>
<td>74</td>
<td>13.8</td>
</tr>
<tr>
<td>Nutritional assessment</td>
<td>Malnourished</td>
<td>7</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Normal weight</td>
<td>128</td>
<td>23.8</td>
</tr>
<tr>
<td></td>
<td>Overweight</td>
<td>202</td>
<td>37.6</td>
</tr>
<tr>
<td></td>
<td>Obese</td>
<td>200</td>
<td>37.3</td>
</tr>
<tr>
<td>Race</td>
<td>White</td>
<td>407</td>
<td>75.8</td>
</tr>
<tr>
<td></td>
<td>Half-Blood</td>
<td>49</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Afro-Cuban</td>
<td>81</td>
<td>15.1</td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td>Normal A1</td>
<td>423</td>
<td>78.8</td>
</tr>
<tr>
<td></td>
<td>Moderate A2</td>
<td>48</td>
<td>8.9</td>
</tr>
<tr>
<td></td>
<td>Grave A3</td>
<td>66</td>
<td>12.3</td>
</tr>
<tr>
<td>Risk factor's</td>
<td>Hypertriglyceridemia</td>
<td>324</td>
<td>60.3</td>
</tr>
<tr>
<td></td>
<td>↑Abdominal circumference</td>
<td>301</td>
<td>57.0</td>
</tr>
<tr>
<td></td>
<td>Hyperglycemia</td>
<td>145</td>
<td>27.0</td>
</tr>
<tr>
<td></td>
<td>Hyperuricemia</td>
<td>86</td>
<td>16.0</td>
</tr>
<tr>
<td></td>
<td>Hypercholesterolemia</td>
<td>49</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td>Smoking</td>
<td>3.4</td>
<td>6.3</td>
</tr>
<tr>
<td></td>
<td>Arterial hypertension</td>
<td>406</td>
<td>75.6</td>
</tr>
<tr>
<td>Associated chronic</td>
<td>No background</td>
<td>109</td>
<td>20.3</td>
</tr>
<tr>
<td>diseases</td>
<td>Ischemic heart disease</td>
<td>90</td>
<td>16.7</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>35</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>Gout</td>
<td>16</td>
<td>3.0</td>
</tr>
</tbody>
</table>

Table 3. Commitment to target organs of the study group.

<table>
<thead>
<tr>
<th>Damage to target organs</th>
<th>Classification</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary sediment</td>
<td>Normal</td>
<td>510</td>
<td>95.0</td>
</tr>
<tr>
<td></td>
<td>Pathological</td>
<td>27</td>
<td>5.0</td>
</tr>
<tr>
<td>Kidney ultrasound</td>
<td>Normal</td>
<td>357</td>
<td>66.5</td>
</tr>
<tr>
<td></td>
<td>Nephrolithiasis</td>
<td>63</td>
<td>11.7</td>
</tr>
<tr>
<td></td>
<td>Pathological</td>
<td>79</td>
<td>14.7</td>
</tr>
<tr>
<td></td>
<td>Kidney cyst</td>
<td>38</td>
<td>7.1</td>
</tr>
<tr>
<td>Eye fundus</td>
<td>Normal</td>
<td>458</td>
<td>85.3</td>
</tr>
<tr>
<td></td>
<td>Pathological</td>
<td>79</td>
<td>14.7</td>
</tr>
</tbody>
</table>

Gomez Y, et al. REV SEN 2023;11(2): Page 149
minuria is defined as >30 mg/g creatinine or 30 mg in 24 hours, while disease during albuminuria, which predicts the development of chronic kidney disease. In this study, 423 cases showed normality in 463 cases (86.2%) of the female sex. Furthermore, in the case of adult older people, in addition to decreasing renal function, a decrease in the glomerular filtration rate of 8 ml/min/decade has been observed. Therefore, in the present study, the highest frequency of disease evolution was found in ages over 60, with 259 cases (48.2%) and in females, with 109 cases (31.5%).

Such results are consistent with what is reported by the medical literature when it reports that from the fourth decade of life, there is a decrease in the glomerular filtration rate of 8 ml/min/decade. However, in the case of adult older people, in addition to decreasing renal mass, a high percentage of sclerosed glomeruli is also observed in direct relation to the passage of time, which, added to the presence of concomitant diseases, are capable of damaging the functional structures of the kidney alone. [9-11].

The values found in the present study coincide with what is described by other international studies when they report that the group over 60 years of age revealed an increase of more than 40% of this disease, as did the female sex, which could be associated with the fact that women attend consultations more frequently. Additionally, in the province where the study was carried out, there is a higher prevalence of the female sex. [12, 13]. Regarding serum creatinine, which showed normality in 463 cases (86.2%), the nutritional assessment was overweight in 202 cases (37.6%) and normal range microalbuminuria in 423 cases (78.8%).

In this regard, diabetic kidney disease can be detected by measuring albuminuria, which predicts the development of chronic kidney disease. [14, 15]. The urinary albumin-creatinine ratio can be measured in an isolated urine sample or 4- or 24-hour urine. Microalbuminuria is defined as >30 mg/g creatinine or 30 mg in 24 hours, while clinical macroalbuminuria is defined as >300 mg/g creatinine or 300 mg in 24 hours; therefore, an abnormal value must be confirmed in at least one additional urine sample within six months. The amount of protein detected will be directly related to the degree of glomerular impairment. It is then inferred that increased albumin excretion is not only a marker of early diabetic kidney disease but also an increased risk of macrovascular disease. [16-21].

It has also been described that there is an association between poor metabolic control of diabetes and the development of microvascular complications such as diabetic nephropathy. However, many patients develop microalbuminuria despite glycemic control, which raises the suspicion that other interacting factors intervene in its development. [22].

According to Osuna et al. 2014, in research aimed at identifying the sociodemographic and clinical characteristics of patients with Type-2 Diabetes mellitus hospitalized in the Internal Medicine Service of the Hospital of San José-Colombia, the poor control of the disease was reflected in various fundamentally identified aspects in low attendance to medical control by the endocrinology specialist 24% and in patients without control by Internal Medicine 36%. Additionally, 46% of patients with diabetes had access to a glomerular, while less than half (39%) carried out adequate self-monitoring.

In the present study, the highest frequency of disease evolution was found in the range of < 1 year, with 270 cases at 50.3%. According to what is reported in the medical literature, a determining aspect in the development of the lesions typical of diabetic kidney disease and its progression is the duration of diabetes. Thus, the finding of diabetic glomerulopathy is more frequent in those patients where diabetes has started earlier in life. At the same time, vascular and tubulointerstitial changes are more characteristic of older patients with a history of proteinuria, renal failure, and long-standing arterial hypertension. [23-25].

Regarding the high prevalence of hypertriglyceridemia, with 324 cases, 60.3%, it is known that hypertriglyceridemia is a frequent epiphenomenon and can precede the appearance of kidney disease in diabetic patients. [26, 27]. Hypertriglyceridemia represents an independent predictor of the incidence of kidney disease, its progression, and its complications in situations where nephropathy already exists. It is inferred, then, that the combination of diabetes mellitus and chronic kidney disease is incredibly potent in terms of the risk of cardiovascular disease, which requires very close control of risk factors. At the same time, it is necessary to address the control of hypertension, dyslipidemia, and weight.

The most prevalent chronic disease accompanying type 2 diabetes was high blood pressure in 75.6% of cases. It has also been described that most people with diabetes without hypertension show some glomerular histopathological changes but retain normal long-term renal function. In contrast, an increase in the presentation of diabetic nephropathy has been found in patients with familial predisposition and arterial hypertension. [29, 30].

It is also inferred that early treatment of high blood pressure is essential in diabetic patients to prevent cardiovascular disease and...
minimize the progression of kidney disease and diabetic retinopathy. To minimize progression, maintaining blood pressure levels below 140/90 mmHg is essential. In patients with systolic blood pressure between 130-139 mmHg or diastolic blood pressure between 80-89 mmHg, lifestyle changes (diet and exercise) should be implemented. Despite hygienic-dietary treatment, pharmacological treatment should be instituted when blood pressure levels are ≥140 mmHg systolic or 90 mmHg diastolic [31].

The majority of patients in this group were overweight and obese (74.9%). There are few specially designed clinical trials on obesity, although data support that reducing weight and fat intake reduces the risk of chronic kidney disease. Treating obesity in patients should be nonpharmacological and consist of physical exercises and a low-calorie diet, following the recommendations in the section corresponding to the established guidelines. Obesity (BMI ≥30 kg/m²) and overweight (BMI 25-30 kg/m²) increase the risk of developing glucose intolerance and type-2 diabetes mellitus at all ages [32].

In the NHS study (Nurses’ Health Studies), excess adiposity was the most potent risk factor for type 2 diabetes. The risk increased as body fat and central adiposity increased: the age-adjusted relative risk for diabetes mellitus was 6.1 times higher for women with BMI >35 kg/m² than for those with BMI <22 kg/m² [33]. The benefit of physical activity in preventing diabetes has been demonstrated in several studies through engagement in moderate and vigorous aerobic physical activity and muscle strengthening activity (toning, yoga, and resistance), which are associated with a lower risk of type 2 diabetes mellitus [34].

The distribution of patients admitted to the Provincial Diabetic Center of Holguin suspected of occult kidney damage was analyzed according to the stage of diabetic kidney disease and the value of the glomerular filtration rate estimated by known formulas, as shown in Figure 1. The most significant deterioration in renal function occurred in stage 2, compared to the estimated glomerular filtration rates, represented in order of frequency by MDRD with 262 cases (48.8%), CKD-EPI with 254 cases (47.3%) and Cockcroft-Gault with 207 cases (38.5%).

Such results correspond with what is reported by the specialized literature that indicates the superiority of abbreviated –MDRD- (Modification of Diet in Renal Disease) compared to other formulas for estimating the usual glomerular filtration rate since it is based on the serum creatinine concentration, which includes as variables (creatinine, age, sex and race, cystatin C or the combination of both); which makes it a reliable, economical, simple and applicable method in clinical laboratories [35-37].

Under this assumption, multiple studies have developed different equations to reliably estimate the glomerular filtration rate. Among the most representative formulas are CKD-EPI, Cockcroft-Gault, and MDRD, derived from the study of dietary modification in nephropathies using glomerular filtration and measured as isotope clearance in more than 1,600 patients. This measurement of GFR means that from the application of these formulas, the existence of a considerable number of patients with occult kidney disease has been evidenced; that is, with serum creatinine levels in the normal range but with glomerular filtration rate levels lower than 60 mL/min/1.73 m² [33, 36].

It has also been described that although some studies use the MDRD equation, it is essential to know the correlation that exists with the Cockcroft-Gault because it has been seen that some patients with a glomerular filtration rate below 60, when the first formula is applied, have great possibilities to obtain the same result when the second is used [6, 37].

In this trajectory, Otero et al. 2005 reported in a study in Spain that 13% of the sample presented occult renal failure using the MDRD equation in people over 18 years of age [38]. In contrast, other studies report that the CKD-EPI equation (Chronic Kidney Disease-Epidemiology Collaboration) provides greater accuracy in its albumin/creatinine ratio because it improves the predictive capacity of glomerular filtration, the prediction of mortality (overall and cardiovascular) and the risk of developing end-stage chronic renal failure; hence, they recommend estimating the glomerular filtration rate for the calculation [39].

From this perspective, Oviedo 2014, in its study on the albuminuria/creatinuria relationship for the detection of occult kidney disease in members of the diabetic club in Riohacha-Ecuador, found that 28.57% presented persistent microalbuminuria which reveals the presence of occult kidney disease in stage III and 71.43% presented kidney disease stage I and II. He concludes that all diabetic people presented nephropathy at some level because when the diabetes disease begins, damage is actually produced at the kidney level even though it is not yet evident [40].

A study's weakness was the absence of hemoglobin measurements intended to verify the presence of anemia in the context of diabetic kidney disease presented in other studies [41]. In light of this research, it is agreed that diabetic kidney disease is a frequent complication of diabetes mellitus in which microalbuminuria is the most direct predictor. Hence, the most effective prevention and treatment measures are adequate glycemic control and pharmacological blockade of the renin-angiotensin axis. However, multidisciplinary work that includes a diabetologist, nephrologist, dietician, and diabetes educator, among other specialists, is the best approach for managing this disease in high-risk patients.

Conclusion

Patients over 60 years of age and females predominated. Calculation of glomerular filtration rate revealed the most significant trend in normal serum creatinine, nutritional assessment overweight and white skin. Diabetes of less than one year of evolution prevailed. The most prevalent factor was hypertriglyceridemia, followed by a pathological increase in abdominal circumference. The majority presented comorbidities associated with arterial hypertension. Damage to target organs was normal in the urinary sediment, kidney ultrasound, and fundus. The highest percentage of patients presented stage-2 deterioration of renal function. It is concluded that the results show a late
diagnosis of kidney disease in diabetic patients who come to the outpatient clinic with some degree of deterioration in kidney function. Therefore, early screening in health areas is essential.

**Abbreviations**

T2DM: Diabetes mellitus type 2.
GFR: Glomerular filtration rate.
CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.
MDRD: Modification of Diet in Renal Disease Study.

**Supplementary information**

Supplementary materials have not been declared.

**Acknowledgments**

Does not apply.

**Author contributions**

Yadelys Gómez Rojas: Data curation, Formal analysis, Funding acquisition, Review, Project administration, Resources, Software, Writing – original draft.
Arturo Arjona Torres: Conceptualization, Supervision, validation, visualization, methodology, Writing – review and editing.
Luis Angel Ros Abreu: Supervision, Validation, Visualization, Methodology, Writing – review and editing.
All the authors have read and approved the final version of the manuscript.

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None of the authors received funding for the present study. The authors paid the administrative expenses of the research.

**References**


**Availability of data or materials**

The data sets generated and analyzed during the current study are not publicly available due to participant confidentiality.

**Statements**

**Ethics committee approval and consent to participate**

The Scientific Council and the Research Ethics Committee of the Vladimir Ilich Lenin Hospital in Holguín, Cuba, approved the research project. The handling of the data collected at all times was confidential and coded. The present research was carried out following the ethical principles outlined in the Declaration of Helsinki, “Recommendations to guide physicians in biomedical research involving human beings,” based on reasonable medical practice adopted by the World Medical Assembly and amended by the 52nd General Assembly in Edinburgh, Scotland in October 2008 and subsequently in 2015, which raises the primacy of life and respect for the dignity of the human being.

**Consent for publication**

Not needed for studies that do not publish patient photographs, tomography scans, or X-ray studies.

**Conflicts of interest**

The authors report having no conflicts of interest.

**Author information**

Not declared.


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