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Original Article

DEMODICOSIS CUTIS AND METABOLIC DISTURBANCES

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Summary

Cutaneous demodicosis (CD) is a pilosebaceous unit disease, overlapping clinically with other facial dermatoses, mainly rosacea, and acne. It is usually improved by acaricidal monotherapy. This study investigates the association of CD with metabolic disturbances. It was conducted with 141 patients with primary and secondary CD. The study investigated the correlation between CD and dyslipidemia based on disturbances in total cholesterol (TC) and Low-Density Lipoproteins (LDL) and between CD and impaired glucose tolerance, diagnosed with elevated fasting blood sugar levels, 120 minutes blood sugar levels in oral glucose tolerance test (OGTT) and the mathematically calculated Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index. The study results were verified with control groups. It was established that patients with CD do not show statistically significant deviations in serum lipoproteins compared with the control group. However, the patients with CD tended to have impaired glucose tolerance, demonstrated with elevated fasting glucose levels and elevated HOMA-IR, compared to the control group. Interestingly enough, the tendency towards prediabetes and diabetes was not confirmed by the 120 minutes blood glucose levels of the OGTT. The presented data confirm the need for testing impaired glucose tolerance in every patient with cutaneous demodicosis. Based on the presented evidence, it is recommended to perform the screening by evaluating fasting glucose levels and fasting insulin levels, followed by calculating the HOMA-IR index.

Keywords: cutaneous demodicosis, rosacea, dyslipidemia, prediabetes, diabetes

Introduction

The cutaneous demodicosis (CD) is a pilosebaceous unit disease associated with the human Demodex mites, affecting mainly the face and head areas. From a clinical point of view, it is divided into primary, unassociated with other facial dermatoses, and secondary, associated with another facial dermatosis [1]. Although cutaneous demodicosis is a distinct disease sui generis, clinically, it often resembles other

facial dermatoses, which leads to confusion in the medical practice and scientific literature. The diseases overlapping with cutaneous demodicosis are acne vulgaris, dermatitis periorificialis, various folliculitis types, and, most importantly, rosacea.

On the other hand, rosacea is a disease known to dermatologists for many years. Currently, under the term rosacea, most dermatologists understand a chronic, inflammatory condition, affecting mainly the centrofacial area, characterized by flushing and persistent erythema [2]. The exact pathogenesis of the rosacea is still unknown, but plenty of evidence supports the theories of dysregulation of the innate immunity and cutaneous neuro-vascular system, genetic factors, microorganisms, and environment as inducing and worsening clinical factors [3].

Rosacea, Demodicosis cutis and metabolic disturbances

A host of publications exist as to the association of rosacea with metabolic disorders (MD) and diseases of other organs and systems, from amongst which Metabolic Syndrome (MS) stands out along with its main symptoms – hypertension, impaired glucose tolerance, and atherogenic dyslipidemia (AD) [4-10].

Over the last several years, a body of clinical, histopathological, and immunological evidence has been amassed to identify specific forms of rosacea (R) and cutaneous demodicosis (CD). It could be said that every condition of facial erythema associated with an abnormal population of human Demodex mites in which visible telangiectasia are not to be detected and/or in which there is no prior medical history of abnormal transient flushing may be categorised as CD and not as R. A multitude of facts are extant in support of this theory. However, perhaps the most fundamental one is the influence on the condition of acaricidal treatment and the lack of influence of vascular laser treatment [11-19].

In the context of the above assertion, it might be considered that a substantial proportion of data concerning R may actually relate to CD. Since R and CD share so many epidemiological mechanisms and clinical characteristics, it is not unlikely that they also share their association with metabolic disorders.

The publications researching the link between CD and MD are significantly fewer than those concerning R because of the lack of nosological clarity regarding the dermatosis in question [20]. In light of the facts we have laid out above, we investigated the association of CD with MD in the form of a retrospective study.

Materials and Methods

Our retrospective study included 141 patients with primary and secondary CD who attended our outpatient practice in 2019 and 2020. The diagnosis was determined by an experienced dermatologist based on a constellation of clinical signs and/or microscopic tests (positive surface skin biopsy of the number of Demodex mites >5 per cm^2) and/or dermatological testing (the presence of opisthosoma and/or gelatinous follicular 'plugs') at the time of the initial examination [1,15,16].

The development of the condition was monitored, with at least one follow-up examination taking place between 30 to 60 days after the initial examination. Confirmation of the diagnosis of CD was derived from the achievement of clinical improvement or cure following the administration of acaricidal treatment.

The patients with CD were divided into two groups depending on the clinical form of the dermatosis. In Group 1 were placed patients with primary cutaneous demodicosis, defined as an abnormal increase in the quantity of Demodex mites in active lesions (in the absence of other accompanying skin disorders with a similar cutaneous morphology such as acne vulgaris, rosacea, dermatitis periorificialis, among others), with the condition also influenced by systemic or local acaricidal monotherapy, without supplementary antibiotic or device-based treatment. Group 2 included patients with secondary cutaneous demodicosis, defined as an abnormal increase in the quantity of Demodex mites along with the presence of underlying facial dermatoses, such as rosacea, acne vulgaris, and dermatitis periorificialis [1].

In the patients with cutaneous demodicosis, laboratory markers for metabolic abnormalities were investigated, namely those associated with the presence of dyslipidemia (LDL, HDL, total

cholesterol), as well as those associated with imposed glucose tolerance (fasting serum insulin, an oral glucose tolerance test, based on which the HOMA-IR index was calculated). Metabolic markers linked to dyslipidemia were chosen because of the proven association with rosacea. [21] Impaired glucose tolerance was defined as insulin resistance accompanied by a HOMA-IR index of over 2.7, as well as prediabetes (with fasting blood glucose (BG) being between 5.6 and 7 mmol/l or at the 120th minute of an oral glucose tolerance test (OGTT, between 7.8 and 11.0 mmol/l) and diabetes (with values for fasting BG being over 7 mmol/l or at the 120th minute of a glucose tolerance test a value above 11.0 mmol/l) [21-25].

The clinical laboratory tests were conducted in the laboratories of Bodimed according to the following set of procedures:

1. A method for the quantitative determination of insulin levels in the serum. We employed a test for electrochemiluminescent immunoassays ‚ECLIA' designed for use with the immunological analyzers Elecsys and Cobas e. The tests were carried out on the automatic immunological analyzer Cobas e 411 using the reagents of Roche Diagnostics. The material for the testing was serum (blood taken with a test tube containing separating gel, which we analyzed immediately, without preceding or subsequent storage of the biological material.

2. Quantitative determination of the biochemical markers - blood sugar, LDL, HDL, and total cholesterol and triglycerides were carried out using the test kits of Roche Diagnostics, designed for use with the clinical chemical analyzer Cobas Integra 400 Plus from the same company. While taking blood for determining the biological markers, we adhered strictly to the requirements for the pre-analytic phase: in the morning, on an empty stomach, between 7.30 and 9.30 a.m. following a 12-14 hour period of fasting and with complete psychological and physical rest. We used vacutainers with separating gel for the serum, which we centrifuged immediately after taking the blood. We did not store the biological material but determined the marker values immediately after the blood separation and prepared the results on the same day. In this way, we avoided the results being influenced by prolonged storage, especially blood sugar. We also avoided all interfering factors (for example, new blood was taken in the case of haemolysed serum).

The data thus obtained was entered and processed. All statistical analyses were performed with IBM SPSS Statistics 25. The following methods were used:

- descriptive statistics for qualitative and quantitative variables
- nonparametric chi-square test with Fischer's Exact Test for hypothesis evaluation
- the Kolmogorov-Smirnov test and the Shapiro-Wilk test in samples with a volume of less than 60 for assessing the normality of the distribution
- the nonparametric Mann-Whitney test to compare independent samples for variables with distributions other than standard and Student's t-test for variables with normal distribution.

A significance level $P < 0.05$ was used to accept statistical significance in all analyses.

Results

Within the study framework, 141 patients aged 7 to 70 were investigated. The average age of the patients with CD was 32.4 years (± 11.9 standard deviation). In the group for primary demodicosis, we placed 86 patients (61%), 66 (76.7%) of whom were women, with an average age of 34.65 years (± 12.1). The group for secondary demodicosis included 35 patients (39%), of whom 41 (74.5%) were women, with an average age of 28.93 years (±10.7).

It is noteworthy that in our study, women with CD (107 or 75.9%) were more than men with CD (34, or 24.1%) (Figure 1) (Table 1). Statistical analysis shows that this difference in the relative proportion of females to males with CD is statistically significant with $P<0.05$ (actual value <0.0001).

As far as age is concerned, the patients with secondary CD were younger than those with primary CD. The data analysis shows that the difference in age between the patients with primary and those with secondary CD was statistically significant. $P>0.05$ (0.0024), both for women: $P>0.05$ (0.013) and for men: $P>0.05$ (0.043), respectively. (Figure 2) (Table 2). The

data analysis showed that the difference in age between the patients with primary and those with secondary CD was statistically significant. P>0.05 (0.0024) for both women: P>0.05 (0.013) and for men: P>0.05 (0.043).

In light of the facts outlined, it may be asserted that, within the group studied, the CD was more frequent amongst women than amongst men, and the patients with secondary CD were younger than those with primary CD. It is also necessary to bear in mind the hypothesis that women with facial problems more often seek dermatological assistance than men with similar pathology. Consequently, further studies are required to confirm or refute these epidemiological trends as regards CD in general.

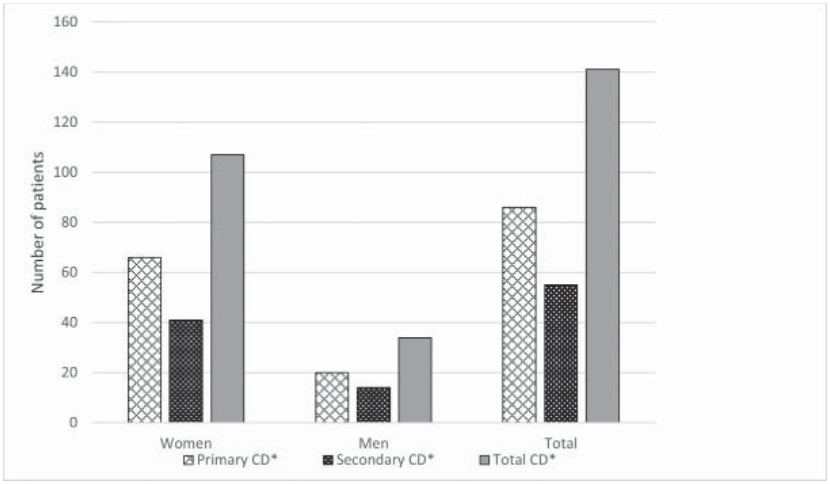

Figure 1. Distribution of patients with CD by gender

Table 1. Distribution of patients with CD by gender

	Women	Men	P-value
Primary CD	66 (76.7%)	20 (23.3%)	**<0.0001**
Secondary CD	41 (74.5%)	14 (25.5%)	**<0.0001**
Total CD	107	34	**<0.0001**

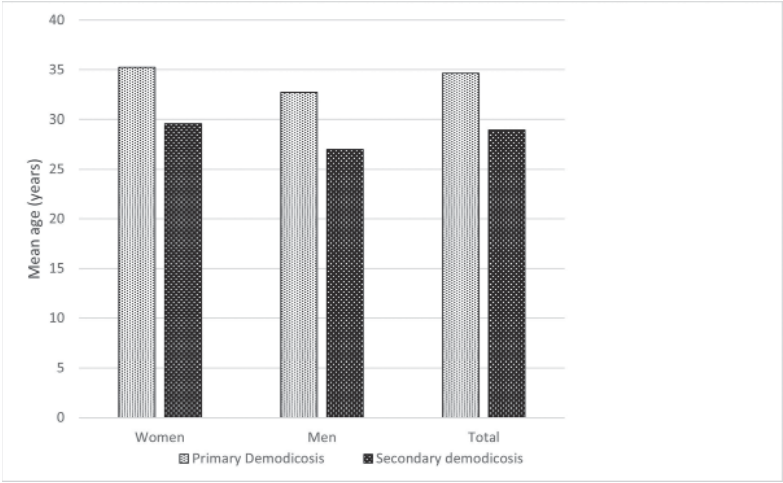

Figure 2. Distribution of patients with CD by age

Table 2. Distribution of patients with CD by age

	Primary CD	Secondary CD	P-value
Women	35.24 (+/- 12.2)	29.6 (+/- 10.4)	0.013
Men	32.7 (+/- 11.7)	27.00 (+/- 11.6)	0.043
Total	34.65 (+/- 12.1)	28.93 (+/- 10.7)	0.0024

Dyslipidemia and glucose tolerance

Total cholesterol and LDL were measured in all the 141 patients in the study. Due to technical difficulties, fasting glucose was measured in 123 patients, while fasting insulin (needed to calculate HOMA-IR) was measured in 102 patients.

Abnormal values for LDL (over 3.36 mmol/l) were recorded in 44.7% of the patients with CD. Abnormal values for total cholesterol (over 5.2 mmol/l) were recorded in 50.4% of the patients with CD (Table 3).

Impaired glucose tolerance, defined as insulin resistance with a HOMA-IR index of over 2.7 and prediabetes/diabetes with values for fasting glucose of over 5.6 mmol/l, was registered in 65.2% and 27.6% of the patients with CD, respectively (Table 3).

The average values for LDL, total cholesterol, and fasting glucose for the patients with CD were LDL - 3.06 (± 0.88) mmol/l, total cholesterol - 4.96 (± 1.05) mmol/l, and fasting glucose - 5.34 (± 0.69) mmol/l (Table 4).

Table 3. Dyslipidemia and glucose tolerance in the control group (CG) and in the patients with CD

Value	Patients in CG with abnormal values	Number of patients in CG	Patients with CD with abnormal values	Number of patients with CD	P-value
LDL>3.36 mmol/l	32%	50	44.7%	141	0.059
Total cholesterol >5.2	44%	50	50.4%	141	0.44
Fasting BG >5.6	14%	50	27.6%	123	0.028
HOMA index > 2.7	20%	50	65.2%	102	<0.0001

Table 4. Average values for LDL and fasting glucose in the control group (CG) and in the patients with CD

Value	Values in CG	Number of patients in CG	Values in CD	Number of patients with CD	P-value
LDL	3.1 (+/- 0.71)	50	3.06 (+/- 0.88)	141	0.62
Total cholesterol	5.22 (+/- 0.86)	50	4.96 (+/- 1.05)	141	0.009
Fasting BG	5.14 (+/- 0.38)	50	5.34 (+/- 0.69)	123	0.002

Discussion

A degree of confusion exists in the literature regarding demodicosis. According to some authors, cutaneous demodicosis in humans does not represent a separate disease unit but rather the increased Demodex mites population accompanying specific inflammatory dermatoses such as the various phenotypic manifestations of rosacea and perioral dermatitis [1-11, 26-28].

Perhaps one of the most precise general statements regarding the place which demodicosis occupies in the dermatological spectrum of pathology comes from a publication by Hay in the British Journal of Dermatology, where it is said that it is reasonable to evaluate the role of the Demodex mites in the pathogenesis of dermatoses, where elimination of the mites leads to clinical remission. "Hence, there is a need for a clinical classification, without which further study of potential pathogenetic mechanisms would be difficult" [26]. Undeniably, the route to a more precise definition of the clinical significance of demodicosis and the most effective therapeutic approach is via clarification of the nosology of the illness, which will allow for a more appropriate diagnosis and selecting a treatment to prescribe.

In 2014, Chen and Plewig suggested a helpful classification of the clinical manifestations of cutaneous demodicosis: spinulate, papulopustular, and conglobate forms [1].

Clinically, spinulate demodicosis manifests with discrete, fine, mottled, or yellowish sharp squames resembling spikes, mainly attached to the follicular openings, though not exclusively,

located on the skin of the face with or without discrete erythema and inflammation. These ‚squames' or spinulae likely represent the opisthosomata (small tails) of the follicular Demodex mites. The changes to the skin are either isolated or grouped [27-29].

The papulopustular form or demodicosic folliculitis is characterised by inflammation concentrated mainly perifollicularly. Morphologically, it may manifest as perifollicular papulopustules or nodules of varying dimensions. Histopathologically, the morphology of the clinical changes to the skin reflects the depth of the pathological process in the skin [30,31]. In the conglobate form, larger inflammatory lesions can be observed in the form of nodules and nodes distributed perifollicularly [30].

Although cutaneous demodicosis mainly affects the face, descriptions are extant of extrafacial forms in immunocompetent and immunocompromised individuals [31-40].

Atherosclerotic cardiovascular diseases (ASCVD) and their clinical manifestations, such as myocardial infarction and ischemic stroke, are a leading cause of death worldwide. A host of evidence exists from meta-analyses and prospective epidemiological studies, which supports the fact that Low-Density Lipoproteins Cholesterol (LDL-C) and impaired glucose tolerance are directly linked to the development of ASCVD. The risk of retention in the immediate vicinity of the blood vessels and the formation of atherosclerotic plaques increases as the concentration of LDL-C in the blood plasma increases in a dose-dependent manner [41]. With this in mind, early diagnosis and treatment of high levels of LDL-C, based on their association with primary and secondary cutaneous demodicosis, especially at an early age, would reduce the incidence of morbidity from ASCVD in the future, thus lessening the burden on the national healthcare system and the mortality from ASCVDs.

Many studies link rosacea with a high level of LDL [10-16, 21, 42-44]. Given the lack of clarity and overlooking the difference between rosacea and CD, we decided to investigate LDL and total cholesterol levels in our group of 141 patients with CD. In the patients with CD, the average values for total cholesterol and LDL were lower both in the control group/CG individuals with similar demographic characteristics and the patients with rosacea. The only differences in values for LDL between CD and control group (CG) were not statistically significant. This observation contradicts the established data in the scientific literature, and its significance and accuracy are to be further clarified [45].

In the analysis of dyslipidemia and glucose tolerance in patients with CD, a control group of 50 individuals with similar demographic characteristics was investigated by Belli AA, God SO, Akbaba G, Etgu F, Dogan G. The relationship between rosacea and insulin resistance and metabolic syndrome was discussed in publications in the European Journal of Dermatology. 2016; 26 (3): 260-264 [21].

When comparing the incidence (44.7%) of abnormal values of LDL (over 3.36 mmol/l) with that of the control group – CG 32% with a value for LDL of over 3.36 mmol/l, the null hypothesis was confirmed, with no statistically significant differences registered: $P>0.05$ (actual value 0.059).

When comparing the incidence of abnormal total cholesterol of the CD group (50.4% with a value for total cholesterol of over 5.2 mmol/l) with that of the control group – CG (44% with a value for total cholesterol of over 5.2 mmol/l), the null hypothesis was confirmed, with no statistically significant differences registered: $P>0.05$ (0.44).

Against the background of these facts, it is possible to postulate that in patients with CD, dyslipidemia is slightly more frequent than in the individuals from the CG with similar demographic characteristics. However, the difference was not statistically significant.

Diabetes mellitus (DM) is a unifying heterogeneous metabolic disorder whose main symptom is chronic hyperglycaemia. The diagnostic criteria for DM include serum fasting glucose of over 7.0 mmol/l or serum glucose at the 120th minute from the start of an oral glucose tolerance test (OGTT) of over 11.1 mmol/l or levels of glycated haemoglobin of over 6.5%. In many cases, the condition is characterized by impaired glucose tolerance (Glucose Tolerance Disorder, GTD), serum fasting glucose of 5.6 to 6.9 mmol/l, or serum glucose at the 120th minute from the start of an OGTT of from 7.8 to 11

mmol/l. It is widely accepted for this condition to be defined as prediabetes, which, apart from an increased risk of developing DM, is associated with microangiopathy, macroangiopathy, and the ensuing renal, ocular, and neurological complications. A similar link exists between prediabetes and metabolic syndrome, cognitive impairment, neoplasms, hormonal disturbances, hepatic steatosis, and obstructive sleep apnea. Apart from this, a level of serum glucose at the 120th minute from the start of an OGTT of 7.8 to 11 mmol/l is associated with increased mortality due to ASCVD [22, 23, 25, 46-48].

According to the World Health Organisation, the diagnosis of prediabetes is based on the following clinical laboratory criteria: serum fasting glucose of from 5.6 to 5.9 mmol/l or serum glucose at the 120th minute OGTT of 7.8 to 11 mmol/l. Several authors have amended this definition, showing increased risk of CM even at levels of serum fasting glucose of from 4.5 to 4.8 mmol/l, while another study has demonstrated that 50% of the patients with serum fasting glucose of over 5.9 mmol/l develop DM. Another clinical laboratory criterion allowing a diagnosis of prediabetes is the fasting level of serum insulin. It is of significance that the treatment of prediabetes is conducted mainly using a change in the type of diet and level of physical activity and, very rarely, through the using medication [25].

The association of rosacea with impaired glucose tolerance is well documented in the scientific literature [6-10,21,42-44]. On the other hand, data about the link between CD and prediabetes and diabetes is sparse [45]. For this reason, we investigated the association between CD with impaired glucose tolerance, defined as insulin resistance with a HOMA-IR index of over 2.7, prediabetes (with fasting glucose of 5.6 to 7 mmol/l or at the 120th minute from the start of an oral glucose tolerance test of 7.8 to 11.0 mmol/l), and diabetes (with values for fasting glucose of over 7 mmol/l or at the 120th from the start of an oral glucose tolerance test of over 11.0 mmol/l) [21-25].

Impaired glucose tolerance, defined as insulin resistance with a HOMA-IR index of over 2.7 and prediabetes/diabetes with values for fasting glucose of over 5.6 mmol/l, was registered in 65.2% and 27.6% of the patients with CD, respectively. Comparison of these values with the control group (20% with a value of the HOMA-IR index of over 2.7 and 14% with a value of fasting glucose of over 5.6 mmol/l) strengthened the alternative hypothesis, demonstrating statistically significant differences with $P<0.05$ (actual measure value 0.0001) for the HOMA-IR index and $P<0.05$ (measured value0.028) for prediabetes/diabetes (values for fasting glucose of over 5.6 mmol/l) (Table 3).

In this sense, it may be asserted that the patients with CD display impaired glucose tolerance more frequently than the control group patients with similar demographic characteristics.

Interestingly, the investigation of glucose tolerance with an OGTT and glucose at the 120th minute supports the conclusions drawn from the HOMA-IR index and fasting glucose levels. The unconfirmed value of the tests regarding the diagnosis of diabetes mellitus, the interpretation of this data is beyond the scope of this article [22,23,46-49].

Comparing the average values for LDL, total cholesterol, and fasting glucose in patients with CD, the control group, and the patients with rosacea produced interesting results [21].

The average values for LDL in patients with CD did not differ from those of healthy patients in the control group, $P>0.05$ (0.62), but they did differ significantly from the group of patients with rosacea, $P<0.05$ (<0.0001), which was lower to a statistically significant degree.

On the other hand, the average values for total

Table 5. Average values for LDL and fasting glucose in the patients with rosacea and CD

Value	Values in rosacea	Number of patients with rosacea	Values in CD	Number of patients with CD	P-value
LDL	3.44 (+/- 0.81)	47	3.06 (+/- 0.88)	141	<0.0001
Total cholesterol	5.65 (+/- 0.86)	47	4.96 (+/- 1.05)	141	<0.0001
Fasting BG	5.37 (+/- 0.73)	47	5.34 (+/- 0.69)	123	0.57

cholesterol in patients with CD were significantly lower than those measured in the control group, P<0.05 (0.009) and those measured in patients with rosacea, P<0.05 (<0.0001), being lower to a statistically significant degree (Table 4).

As regards glucose tolerance, the average values for fasting glucose in patients with CD were lower to a statistically significant degree than those of the control group (P<0.05 (0.002), but do not differ from those for patients with rosacea, and P>0.05 (0.57). (Table 5)

Against the background of these facts, it is possible to conclude that in patients with CD, the average values for total cholesterol and LDL were lower, both in comparison with individuals in the control group with similar demographic characteristics and in comparison with the patients with rosacea. Only the differences in values for LDL between the patients with CD and the control group were not statistically significant.

On the other hand, the average values for fasting glucose in patients with CD were statistically higher than those of the control group individuals with similar demographic characteristics, though they did not differ from the average values for fasting glucose in the patients with rosacea.

Given the apparent tendency to impaired glucose tolerance in patients with CD, we decided to compare the number of the patients in the group studied with prediabetes and diabetes, diagnosed employing the 'Gold Standard' in endocrinology – OGTT (values for glucose at the 120th minute of the glucose load), with the established incidence of the conditions in the population at large [23].

It turned out that, despite the established tendency towards impaired glucose tolerance in the CD patients, including statistically significant differences from the control group with P<0.05 (0.0001 measured value) for the HOMA-IR index and P<0.05, measured value 0.028, for prediabetes/diabetes values for fasting glucose of over 5.6 mmol/l), the patients with CD and prediabetes/diabetes, diagnosed using OGTT (values for glucose at the 120th minute of the glucose load) were significantly fewer than those in the control group - P<0.05(<0.0001) (Table 6, Table 7).

Table 6. Impaired glucose tolerance diagnosed by means of OGTT

Value	Number in CG	% in CG	Number of CD	% CD	P-value
Prediabetes	1221/7412	16.4%	8/109	7.3%	0.01
Diabetes	513/7412	6.9%	3/109	2.8%	0.04
Prediabetes and Diabetes	1734/7412	23.4%	11/109	10.1%	<0.0001

Table 7. Lipid profile and glucose tolerance in patients with rosacea (R), CD and the control group (CG)

Value	R	R-number	CG	CG-Number	P-R/CG	CD	CD-Number	P-CD/CG
LDL>3.36 mmol/l	48.9%	47	32%	50	0.089	44.7%	141	0.059
Total cholesterol>5.2	72.3%	47	44%	**50**	**0.005**	50.4%	141	0.44
Fasting blood glucose >5.6	38.2%	47	14%	**50**	**0.006**	27.6%	123	0.028
HOMA index > 2.7	44.7%	47	20%	**50**	**0.009**	65.2%	102	<0.0001

Conclusions

Based on the data presented, it may be concluded that CD can be seen either as a separate dermatosis or in the context of another underlying facial dermatosis. The diagnosis and treatment of CD are severely impeded by the lack of clear clinical criteria for primary and secondary demodicosis. The most considerable difficulty is encountered in the case of secondary demodicosis, where the morphological overlapping with other facial dermatoses (acne

vulgaris, dermatitis, periorificialis, various types of folliculitis, and, most of all, rosacea) hinder practicing dermatologists. In these cases, we suggest that the following be regarded as a diagnostic symptom in the case of rosacea: the presence of transient erythema preceding the illness and centrofacial telangiectasia; and in the case of acne: open and closed comedones.

This retrospective study showed a clear association of CD with impaired glucose tolerance, though not with atherogenic dyslipidemia. For this reason, the routine testing of serum insulin and fasting glucose in all patients with CD is a key to the early diagnosis and treatment of diabetes and prediabetes.

We think that primary and secondary demodicosis may even be seen as a very early dermatological marker of a prediabetic or diabetic condition. Confirming a positive association of primary and secondary demodicosis with prediabetes or full diabetes mellitus would allow early diagnosis and timely treatment involving a change in lifestyle and/or medication, which can prevent the severe and life-threatening complications of these socially significant diseases.

The study we conducted clearly showed the gaps in the scientific literature concerning the clinical criteria for cutaneous demodicosis and rosacea and their association with metabolic disorders. Further wide-ranging studies to research these two aspects of the conditions are of the utmost necessity. On the one hand, studies may help determine how cutaneous demodicosis and rosacea can be clinically differentiated and in which cases this is required. On the other hand, further research into the association of cutaneous demodicosis with metabolic disorders and finding answers to questions whether the metabolic balance influences the clinical presentation of CD or CD may be considered an early indication of metabolic syndrome.

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