The Correlation Between Hyperglycemia and Rheumatoid Factor in Type 2 Diabetic Patients in Al- Risafa Area, Baghdad

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Abstract

Diabetes mellitus type 2 (T2DM) formerly called non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes is a common disease**.** Rheumatoid factor is a well-established test used in the diagnosis and follows the prognosis of rheumatoid arthritis (RA). Rheumatoid factor is sometimes found in serum of patients with other diseases including diabetes mellitus (DM), due to the presence of pro-inflammatory cytokines such as TNF- α which play an important role in chronic inflammatory and autoimmune diseases like rheumatoid arthritis (RA). The aim of the study is to investigate the associations between type 2 diabetes mellitus (T2DM) and rheumatoid arthritis (RA) in scope of rheumatoid factor (RF), hyperglycemia and body mass index (BMI), in patients with T2DM lived in Al-Risafa area -Baghdad. One hundred twenty five (125) type 2 diabetes mellitus (T2DM) patients were selected from the out patients department of the Specialized Center for Endocrinology and Diabetes, Baghdad; in addition to (70) apparently healthy non diabetic, non arthritic subjects as control, during the period from Sep. - Dec./2010. The ages of both patients and control subjects were within (35-75) years. This study focus to search for the correlation between T2DM and RF "qualitative and quantitative" in relation to body mass index (BMI) and gender. Out of 125 DM-patients (73 female and 52 male), 44 (35.2 %) showed positive RF when compared with healthy controls (N=3, 4.3%). [P value =0.01 is significant] with female dominance (N=28, 63.6%) in compared to males (N=16, 36.4 %), when these diabetics with RF positive were titered for RF (8, 16, 32 and 64 IU/ml), the following results were obtained. The highest percentage of titer observed with 34.1% in those with RF titer 64 IU/ ml [P value = 0.01] when compared with healthy control. 18.2 % had RF titer of 8 IU/ ml, 20.4 % had RF titer of 16 IU/ ml, 27.3 % had RF titer of 32 IU/ ml and 34.1 % had RF titer of 64 IU/ ml. The highest percentage among the overweight, DM patients (38.9 %) have a mean titer 64 IU/ml, a percentage decrease respectively as below: 38.9 % had RF titer of 64 IU/ ml, 27.8% had RF titer of 32 IU/ ml, 16.6 % had RF titer 16 IU / ml and 16.6% had RF titer 8 IU/ ml. The highest number and percentage of DM with RF positive (N=17, 38.6 %) were located among higher age (50-59), (60-69) & (70 -79) year groups (N=17, 38.6%), (N=13, 29.5%) & (N=8, 18.2%) respectively, [P- Value < 0.01] when compared to the corresponding controls. The effect of fasting plasma glucose level of type 2 DM in patients who have RF positive titer, is found that ≥ 7.2 mmol/l glucose in plasma contribute the highest titer (N=28, 63.6 %), in comparison with group of plasma glucose levels < 7.2 mmol/l patients (N=16, 36.4%). with a highly significant difference, P-value = 0.006.Smokers diabetic patients with RF positive (N=27, 61.4%) dominate over non- smokers with RF positive (N=17, 38.6%). The results of this study indicate that there is a reasonable increased frequency of positive rheumatoid factor (RF) in type 2 diabetic patients. Poor glycemic control is associated with higher RF titer in positive cases. The titer of T2DM smoker patients is associated with positive RF values that exceed the titer of the non- smoker RF positive patients. Thus, smoking might not be correlated significantly to DM, but may contribute to its complications.

Key words: T2DM, RF, BMI, Smoking.

العلاقة بين ارتفاع السكر عند مرضى السكري- النوع الثاني وظهور العامل الرثواني في منطقة الرصافه - بغداد

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الخلاصة

يُعد مرض السكري النوع الثاني Type 2 diabetes mellitus (T2DM) الذي كان يسمى سابقا داء السكري الغير معتمد على الانسولين (NIDDM) أو سكري البالغين من الامراض الشائعة وأن فحص العامل الرثوي RF يستخدم للتحقق من تشخيص تطور مرض المفاصل الرثواني (Rheumatoid Arthritis (RA يلاحظ ايجابية هذا النوع من التحليل RF لكثير من الامراض يضمنها السكري وذلك لوجود مسببات الالتهاب السايتوكين cytokine مثل (TNF- α) التي تلعب دورا مهما في الالتهاب المزمن وامراض المناعه الذاتيه كمرض الالتهاب الرثواني RA وكذلك يرتبط هذا السايتوكين cytokine بالسمنه ومقاومة الانسولين.أخترنا مائه وخمسة وعشرون (١٢٥) مريضا أثبت أنهم يعانون من مرض السكري- النوع الثاني Type 2 Diabetes Mellitus (T2DM) من مراجعي المركز التخصصي للغدد الصم والسكري في منطقة الرصافه- ببغداد ، إضَافة إلى (٧٠) سليماً بالظاهر مع التدقيق أنهم غير مصابين بالسكري ولا يحملون العامل الرثواني Rheumatoid Factor (RF) كمجموعة سيطرة.

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أُدخل هؤلاء الأشخاص في هذه الدراسة لتحري العلا قه بين مرض السكري النوع الثاني والتهاب المفاصل الرثواني ، Rheumatoid Arthritis (RA) باستعمال العامل الرثواني Rheumatoid Factor (RF) (نوعاً وكمّاً) (qualitative & quantitative) وعلاقتهما بمعامل كتلة الجسم Body Mass Index (BMI). أُجري البحث خلال أربعة أشهر (أيلول- كانون الأول ٢٠١٠) وكانت أعمار المرضى وكذلك مجموعه السيطرة تتراوح بين (٣٥- ٧٥) عام. من مجموع مرضى السكري وعددهم ١٢٥تبين أن ٤٤ مريض أي(٣٥.٢%) منهم قد أظهر العامل الرثواني موجباً بالمقارنة مع مجموعة السيطرة وعددهم ٣ أي (٤.٣%).مع نسبة ملحوظة إحصائيا. [P= 0.01] . وكانت إصابة النساء بالعامل الرثواني أكثر من إصابة الرجال ٢٨ مريضه أي (٦٣.٦%) إلى ١٦ مريض أي (٣٦.٤%) على التوالي. عند فحص هؤلاء الذين أظهروا ايجابية العامل الرثواني بالطريقة الكميّه quantitative لدرجة العامل الرثواني ، لوحظ ما يلي : ٣٤.١% منهم أظهر درجة المعايره 64 IU/ ml و ٢٧.٣% منهم أظهر درجة المعايره ٣٢ IU/ ml و ٤و٢٠% منهم أظهر درجة المعايره 16 IU/ml و ١٨.٢% منهم أظهر درجة المعايره 8 IU/ ml . أن أعلى نسبه من هؤلاء المرضى كانوا ضمن مجموعة العامل الرثواني ذي درجة الكم 64 IU/ ml ، ومن ثم تقل على التعاقب. [زيادة ملحوظة0.01 =P.]. أظهر أغلب البدينين من مرضى السكري هم ضمن مجموعة overweight BMI (٣٨.٩%) معايره عالياً من العامل الرثواني (64 IU/ml) والباقون ظهروا على التعاقب. ٣٨.٩ % منهم أظهر درجة معايره 64 IU/ ml و ٢٧.٨ % منهم أظهر درجة معايره ٣٢ IU/ ml و ١٦,٦ % منهم أظهر درجة معايره 16 IU/ ml و ١٦.٦% منهم أظهر درجة معايره 8 IU/ ml . إن أعلى عدد ونسبه من مرضى السكري والمظهري العامل الرثواني كانوا ضمن مجموعة الأعمار العالية(٥٠-٥٩) و(٦٠-٦٩) و(٧٠-٧٩) عام ونسبتهم (١٧ مريض، ٣٨.٦ %) و(١٣مريض، ٢٩.٥%) و (٨ مرضى، ١٨.٢ %) على التعاقب. أن نسبه مرضى السكري بدون سيطرة والذي يكون فيه سكر الدم $\geq$ ٧.٢ ملي مول لكل لتر والذين لديهم العمل الرثواني (٢٨ ، ٦٣,٦ %) أكبر من نسبة المرض السكري المسيطر عليه < ٧.٢ ملي مول لكل لتر والذين لديهم العمل الرثواني (١٦ ، ٣٦,٤) . إن المدخنين المصابين بالسكري والمظهري العامل الرثواني (٢٧ مريض ، ٦١.٤%) كانوا اكثر من غير المدخنين المصابين بالسكري والمظهري العامل الرثواني (١٧مريض ، ٣٨.٦%).ومن ناحيه أخرى أن عدد غير المدخنين المصابين بالسكري وليس لديهم العامل الرثواني (٦٣ مريض، ٧٧.٨%) أكثر من المدخنين وليس لديهم العامل الرثواني (١٨ مريض ، ٢٢.٢%).(زيادة ملحوظة عاليه p.v= 0.000001). نتائج هذه الدراسه تثبت أن هنالك زياده معقوله ايجابية في ظهور العامل الرثواني لدى مرضى السكري - النوع الثاني. ويرتبط ضعف السيطرة على نسبة السكر في الدم مع ارتفاع معيار التردد الرثواني في الحالات الايجابية. ان معيار ايجابية العامل الرثواني في المدخنين والمصابين بالسكري أكثر من غير المدخنين والمصابين بالسكري لهذا فان التدخين قد لا يرتبط مباشره بالسكري وامراض المفاصل الرثوي كمرض وانما بالتاكيد ذات صله بهما.

الكلمات المفتاحية : مرضى السكري النوع الثاني ,RF, BMI ، التدخين

Introduction

Type 2 diabetes mellitus (T2DM) which was formerly called non-insulin dependent diabetes mellitus (NIDDM) or adult-onset diabetes, is a metabolic disorder that is characterized by high blood glucose level [(1)].In T2DM, insulin concentrations may be normal or even high, there is insensitivity of the tissues to the effects of insulin(an effect termed insulin resistance) [(2)].Type 2 DM (T2DM) occurs as a result of chronic insulin resistance and subsequent beta-cell dysfunction that appears to be reversible, particularly in the early stages of the disease [(3)]. Type 2 diabetes, is characterized by progressive insulin resistance that typically accompanies advancing age, inactivity, and weight gain [(4)].

Rheumatoid factor (RF)

Rheumatoid factor is an anti-imunglobulin with a course against fragment Fc of IgG human molecule. Rheumatoid factor is present in (70-80 %) of patients with rheumatoid arthritis (RA), where the disease is defined as a seropositive athropathy [(5)].The RFs frequently occur in a variety of other diseases such as, systemic lupus erythromatus (SLE) (15-35%), systemic sclerosis (20-30%), juvenile rheumatoid (7-30%), poliomyelitis (5-10%) and infection (0-5%) [(6)]. Rheumatoid factor is a well-established test used in the diagnosis and prognosis of rheumatoid arthritis (RA) [(7)]. In addition, rheumatoid factor precedes the appearance of rheumatoid arthritis. Rheumatoid factor is sometimes found in serum of patients with other diseases including diabetes mellitus (DM), due to the presence of pro-inflammatory cytokines such as TNF- α which play an important role in chronic inflammatory and autoimmune diseases like rheumatoid arthritis (RA). The TNF- α has also been closely linked to obesity and insulin resistance [(8)].Substantial studies have been conducted in several Iraqi regions, however; this study was planned to investigate the possible association between T2DM and RF in relation to BMI, age and smoking in Al-Risafa Baghdad area.

Material and Methods

One hundred twenty five (125) patients with T2DM were attending the Specialized Center for Endocrinology and Diabetes, at Al-Risafa, Baghdad, during the period from September to December/ 2010.Age ranging between (35–75) years. In addition to seventy (70) age matched apparently healthy persons as controls, were selected from neighbours, friends and staff members of the college and who attended Al-Kindy General Hospital for checking. Their fasting plasma glucose (FPG) was within the normal range. All plasma specimens were submitted to fasting plasma glucose by enzymatic colorimetric method and Rf – latex by slide agglutination test.

Assay methods

1. ***Blood glucose determination (Enzymatic).***
   Enzymatic, colorimetric method, based on glucose oxidase with reference for serum or plasma in fasting state [(9)]
   Reference value of : 4.2-6.4 mmol/l
   75-115 mg/dl
2. ***Qualitative determination of rheumatoid factor [latex slide agglutination]***
   Principle of method: The RF- latex is a slide agglutination test for the qualitative and semi-qualitative detection of RF titer in human serum. Latex particles coated with human E-globulin are agglutinated when mixed with sample

containing RF. The test occurs by using a kit (Omega Diagnostics AVITEX RF).UK.

Calibration

The RF-latex sensitivity is a calibration against the Word Health Organization (WHO) 1/64 Rheumatoid Arthritis serum.

Sample

Fresh serum should be used to detect measurable titer of anti-IgG (Rheumatoid Factor).

Reading and interpretation

The presence or absence of visible agglutination was observed by necked eye immediately after removing the slide from the rotator.

Semi-quantitative determination

The semi-quantitative test was performed in the same way as the qualitative test using dilution of the serum with phosphate buffered saline as follows

Statistical analysis

The parameters were treated and computerized by using SPSS version 15. P value < 0.05 is considered significant, while P value > 0.05 is considered non significant.

Dilutions	1/2	1/4	1/8
Saline	50 µl	50 µl	50 µl
Serum	50 µl	—	—
Dilution serum 1/2	—	50 µl	—
Dilution serum 1/4	—	—	50 µl
8 x No of dilution	8x2	8x4	8x8
IU/ml	16	32	64

Results

Out of diabetic patients, 44 (35.2%) are positive for RF, 16(36.4%) males and 28(63.6%) females, respectively. While the number and percentage of RF positive subjects out of healthy control are only 3 (4.3%), 1(33.33%) male and 2(66.66%) females, respectively. The differences are significant (P= 0.01).

Table 1: Distribution of studied groups according to RF agglutination test

	Diabetes mellitus patient				Healthy control				Comparison of significant
Gender / RF	Male	Female	Total	Percent	Male	Female	Total	Percent	
Positive	16	28	44	35.2%	1	2	3	4.3%	P= 0.01
Negative	36	45	81	64.8%	29	38	67	95.7%	
Total	52	73	125	100%	30	40	70	100%	

Table (2) shows the comparison of T2 DM patients & healthy control with RF positive in addition to RF negative according to their BMI(kg/m^2).The largest number and percentage of T2DM patients are the overweight patients 47 (37.6%). And when added to obese groups the total will be 108(86.4%).While the largest number and percentage for the control lie in the normal group of BMI 50 (71.4%), with a highly significant difference, P value < 0.01 between BMI and RF in DM as well as in control

Table 2: Comparison of diabetic patients with healthy control who have RF positive and negative according to body mass index BMI (kg/m^2)

	Diabetes mellitus patient				Healthy control				Comparison of significant
RF / BMI	Positive (N=44)	Negative (N=81)	Total (N=125)	Percent	Positive (N=3)	Negative (N=67)	Total (N=70)	Percent	
Under weight 16.5-18.4	0	3	3	2.4 %	0	0	0	0%	P < 0.01
Normal 18.5-24.9	0	14	14	11.2 %	0	50	50	71.4 %	
Overweight 25.0-29	18	29	47	37.6 %	1	14	15	21.4 %	
Obese class I 30.0- 34.9	12	16	28	22.4%	2	3	5	7.1 %	
Obese class II 35 - 40	10	12	22	17.6 %	0	0	0	0 %	
Obese class III Over 40	4	7	11	8.8 %	0	0	0	0 %	
Total	44	81	125	100%	3	67	70	100 %	

Table 3: Distribution of diabetic patients who have RF positive and negative within age groups (years) compared with healthy control.

	Diabetes mellitus patient				Healthy control				Comparison of significant
RF / Age	Positive (N=44)	Negative (N=81)	Total (N=125)	Percent	Positive (N=3)	Negative (N=67)	Total (N=70)	Percent	
30-39	0	6	6	4.8%	0	7	7	10.0%	
40-49	6	22	28	22.4%	0	21	21	30%	P =0.00l8
50-59	17	26	43	34.4%	1	25	26	37.1%	
60-69	13	18	31	24.8%	2	9	11	15.7%	
70-79	8	9	17	13.6%	0	5	5	7.1%	
Total	44	81	125	100%	3	67	70	100%	

Table (3) shows that the highest number and percent of T2DM with RF positive values are located within the age group (50-59) years. At the same age, healthy controls show also the highest number and percent. (P- Value =0.00l8)

Table 4:Distribution of diabetic patients who have RF positive according to their glycemic control and RF titer.

RF titers / Glycemic Control level	8	16	32	64	Total	Percent	Comparison of significant
FPG ≥ 7.2 mmol/l ≥ (130 mg/dl)	2	5	9	12	28	63.6%	P = 0.006
FPG < 7.2 mmol/l < (130 mg/dl)	6	4	3	3	16	36.4%	
Total	8	9	12	15	44	100%	

Table (4) summarizes the effect of fasting plasma glucose level of type 2 DM in relation to RF titer. It is found that ≥ 7.2 mmol/l glucose in plasma contribute the highest titer (N=28, 63.6 %), in comparison with group of plasma glucose levels < 7.2 mmol/l patients (N=16, 36.4%). with a highly significant difference, P-value = 0.006.

Table 5: Distribution of diabetic patients with RF positive according to their titer, in relationship to body mass index groups BMI (kg/m^2)

RF Titers IU/ml / BMI	8	16	32	64	Total	Percent
Under weight 16.5-18.4	0	0	0	0	0	0%
Normal 18.5-24.9	0	0	0	0	0	0%
Overweight 25.0-29	3	3	5	7	18	40.9%
Obese class I 30.0- 34.9	4	3	3	4	14	31.8%
Obese class II 35 - 40	1	2	3	2	8	18.2%
Obese class III Over 40	0	1	1	2	4	9.1%
Total	8	9	12	15	44	100%

As indicated in table (5) it could be conclude the following two points.

Most of type 2 DM patients show RF positive (34.1%) high titer in 64 IU/ml:

Titer (IU/ml)	Number	Percent
64	15	34.1 %
32	12	27.3 %
16	9	20.4 %
8	8	18.2 %

Most of overweight patients show high titer 64 IU/ml: (38.9 %)

Titer (IU/ml)	Number	Percent
64	7	38.9 %
32	5	27.8%
16	3	16.6 %
8	3	16.6%

Table 6: Distribution of smokers among diabetic patients with either RF positive or RF negative results

RF / Smoke	Positive	Negative	Total	Percent	Comparison of significant
Positive	27 (61.4%)	18 (22.2%)	45	36.0%	P= 0.000001 HS
Negative	17 (38.6%)	63 (77.8%)	80	64.0%	
Total	44 (100%)	81 100%)	125	100 %	

A shown in table (6) smokers with RF positive T2 DM patients (N=27, 61.4%), dominate over the non- smoker patients. The non smoker's diabetic patients who have RF negative (N=63, 77.8%) are nearly four times as many as smokers (N=18, 22.2%).

Table 7: Distribution of RF positive diabetic patients according to smoking habit and RF titer

RF Titer IU/ml / Smoke	8	16	32	64	Total	Percent	Comparison of significant
Positive	4	5	8	10	27	61.4%	P= 0.000001 HS
Negative	4	4	4	5	17	38.6%	
Total	8	9	12	15	44	100%	

Table (7) explains the effect of smoking on T2DM/RF positive patients where the smokers are doubling as many as the non- smokers, in titers 32 & 64 IU/ml, and the smoker's numbers are more than the non-smokers (4:4, 5:4, 8:4, and 10:5; total 27:17). The number of patients increases as the titer increases.

Discussion

This work shows that about (35.2%) of the Iraqi population sample (125 subjects) diabetic patients in Al-Risafa region have RF positive in their blood when compared with apparently normal subjects (4.3%) as referred in table (1). These percentages coincide with the results obtained by Moustschen [(10)] in 1992.Also coincide with searches done by Al-Gharawi at 2009, in Medical City, Baghdad, who observed that 62.5% out of DM patients showed RF positive [(11)]; 49% have been recorded in Al-Umara City by Khalawi [(12)] and 15.5% have been reported in Al-Adhamiya, Baghdad City by Al-Hammami [(13)].The differences are possibly due to geographical reason and because the attendants of the Medical City are collection from different districts and most severely diseased. Umara & A'dhamyah are confined areas. Also they have different lifestyles, types of food & behavior. The result of this study (35.2%) RF positive DM patients seem to be affected by the same reasons stated above, and lie in between the results of the other authors. Table (1) shows that 28 females and 16 males had RF positive (approximately 2:1 ratio) which coincides with the work that showed the women presented with RA more often than men, with a ratio of 3:1 [(14)], indicating that hormone levels are of importance [(15)]. Epidemiological and immunological evidence share suggested that female sex hormones could play a role in the etiology and course of chronic inflammatory diseases because of the menstrual cycle, pregnancy, and menopausal status which are important influencing factors [(16)]. Table (2) shows the prevalence of T2DM with RF positive according to their BMI. A significantly higher level concentrated at overweight and obese groups. The T2DM is associated strongly with overweight, independent of age, gender and family history of DM. This relationship has been found consistently in other populations. [(17-21)] Diabetes mellitus and RA are associated with an adverse cardiovascular risk profile, particularly dyslipidaemia [(22, 23)] and obesity is a state of low- grade chronic inflammation, as indicated by the increased concentrations of C-reactive protein, IL-6, and other inflammatory markers identified in the plasma of obese individuals [(24,25)]. Indeed, pro-inflammatory cytokines (TNF-α, IL-18, IL-6) were found to be increased in patients with T2DM. [(26, 27)] The TNF-α, a pivotal pro-inflammatory cytokine in RA, arises from adipose tissue during chronic hyperglycemia in T2DM and has harmful effects on the pathway of insulin signaling. [(28)] The coincidence of BMI level and severity of T2DM resembles the work which concluded that obesity is well recognized as important risk factor for T2DM and impaired glucose tolerance [(29, 30)]. Parallel to this idea, in same table (2) which shows that the positive RF is concentrated in the overweight and obese; while all of the normal BMI(patients & control) had negative RF.Table (3) shows that increased number of T2DM patients who have RF positive are aged 50 and older, which resembles that of the American Diabetes Association (ADA), showing that approximately 18.3% (8.6 million) of the Americans aged 60 and older have diabetes [(31)]and T2DM patients are at ages (40-70) years, which coincide with other workers[(32,33)].Diabetes mellitus in these tables show that the prevalence increases

with age. In a previous review, female's dominant over males explain by the role of the menopause on pro-inflammatory cytokine activity[34].This review focused on the increase of pro-inflammatory cytokines with the menopause (the fall of estrogens and other gonadal steroids), another review on gonadal steroids and T and B cell immunity was presented 10 years ago, but since then, a lot of new information has been generated [35]. This is particularly true with respect to chronic diseases that formerly have not been allocated to "inflammatory diseases" such as bone resorption. This is important because rate of incidence over age for osteoporosis almost matches incidence rates of inflammatory markers, as rheumatoid arthritis (RA). Table (4) shows that most of diabetic patients who have RF positive (N=28 , 63.6%) lie within FPG ≥ 7.2 mmol/l category in comparison with those with lower FPG (N=16 , 36.4%) which lie in FPG < 7.2 mmol/l. These results agree with other workers who showed that 68% of DM patients had FPG ≥ 11.1 mmol/l and 32% of them had FPG < 11.1 mmol/l [13].Glucose intolerance Table (5), presents in RA and diabetes, is another parallel, and indicator for direct correlation between the degree of impaired glucose handling and inflammation [36]. The diabetic patients who have RF positive titer, which mean the severity of disease go parallel with the increase of RF titers. Comparatively, the RF in blood of the control, 4.3%, is too near to the international ratio, 3 %. In this study the results are in agreement with several studies have discussed the association between chronic inflammatory disease states and disorders in intermediary metabolism [37-41], in particular, peripheral insulin resistance (IR).The overweight groups also gain the highest score (38.9%) among the highest RF positive titer, the 44 diabetic with RF positive value agrees with other studies [12, 13].Tables (6 and 7) show the prevalence of T2DM smokers over T2DM non-smokers to have RF positive. Issues of smoking and diabetes are correlated effectively in the ADA technical review [42], it is concluded that smoking might not be the causative agent for T2DM, but definitely is related to it. These tables also show the prevalence of RF positive in smokers over non-smokers, accordingly this model explains that RA results from a complex gene–environment interaction, in which RA only develops after the immune systems has been triggered by several environmental factors, a process which may take years [43]. One of the environmental factors that have been clearly shown to trigger RA is smoking [44].

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