New onset diabetes following exposure to Covid-19 antigen in a cohort of Jordanian population

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ABSTRACT

Background: Hyperglycemia has been described during acute infection with SARS-COV-2 and may persist after the resolution of the acute infection in the form of new-onset diabetes, as a result of several interacting mechanisms.
There have also been several reports of new onset hyperglycemia after exposure to Covid-19 vaccine, however no causal relationship has been established as yet.

Aim: Our aim is to analyze whether exposure to covid-19 antigen is associated with new onset diabetes, and whether the characteristics of new onset diabetes after being exposed to covid-19 antigen (through recent infection or vaccination) differ from patients with new onset diabetes who were not exposed.

Methods: This is a retrospective cross-sectional study, including all patients aged 14 and above who presented to the outpatient diabetes clinic of King Hussein Medical Center with new onset diabetes from January 2021 through March 2022. A form was filled with the patient's data and blood samples were taken for biochemical marker and antibody detection.
Patients were then divided to two groups , those whose exposure to covid-19 antigen is recent (<3 months)were designated to group I, and those who were not exposed or their exposure dates more than 3 months from the onset of the symptoms were assigned to group II.

Results: Group I patients were less likely to have a positive family history or autoantibodies related to diabetes than Group II patients. Also the average C-peptide for group I was elevated compared to Group II(2.97 +/-1.09 vs 1.94 +/- 0.7) , p value 0.000.
Conclusion: Patients who were recently exposed to covid-19 antigen had less risk factors predisposing to diabetes and were found to have higher C-peptide than those whose exposure dates more than 3 months before the onset of their diabetes or were unexposed to covid-19 antigen. This may suggest an independent association between Covid-19 exposure and new onset diabetes that persists well after resolution of the infection.

Keywords: diabetes, hyperglycemia, Covid-19, new onset hyperglycemia , Covid-19 antigen.
MS April 2023; 30 (1):10.12816/0061496

Introduction

Impaired glucose metabolism has been described during acute illness, and is commonly associated with worse outcomes and a more severe course of the disease.

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Submission date:29 May 2022 Acceptance date: 1 December 2022 Publication date: April 2023

[1] New onset diabetes that persists after the resolution of acute illness has also been observed with viral infections and acute illnesses.[2]
A Meta-analysis indicates that enterovirus was significantly associated with T1DM autoimmunity.[3] Also increased risk of Type 2 diabetes has been reported in patients with chronic hepatitis C infection.[4]
The severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) is a member of the coronaviridaefamily, and the causative agent of Covid-19 pneumonia.[5]Making it's first appearance in a local business market in Wuhan, China, on December 2019 (hence the name Covid-19), the virus rapidly spread to cause a pandemic with tremendous healthcare and economic consequences, claiming the lives of more than 6 million people till the date of writing.[6]
Coronaviridae have been associated with diabetes in the past, as is the case with severe acute respiratory syndrome virus (SARS) , which was responsible for the 2002-2004 SARS outbreak. Acute diabetes was commonly present in SARS patients without prior history of diabetes and without using glucocorticoids, and it was considered an independent predictor for mortality in SARS patients. The probable mechanism is through binding of SARS coronavirus to the angiotensin-converting enzyme 2 (ACE2) receptor in the pancreatic islet cells causing damage and eventually reduced insulin secretion.[7] Supporting evidence is that *ACE2* gene knockout mice (KO) had a selective reduction in first phase insulin secretion compared to age matched wild type (WT) mice. KO mice also demonstrated progressive impairment of glucose tolerance, however their peripheral tissue sensitivity to insulin was unchanged compared with WT mice.[8]
SARS-COV-2 utilizes the same ACE-2 receptor to gain entry into the host cell asit's predecessor SARS, and this may be the mechanism of new onset diabetes observed in infected patients who exhibit impaired glucose metabolism.[5] However there are several other interacting mechanisms that may play role in the pathogenesis of glycemic dysregulation in these individuals. These are discussed in further detail in the literature review section that follows.

LITERATURE REVIEW

Pre-existing diabetes

Some individuals who manifest new onset diabetes during their Covid-19 infection which persists after their recovery may actually have pre-existing undiagnosed diabetes, bearing in mind the major changes in lifestyle (ie less physical activity and weight gain) due to lockdown policies leading to increased insulin resistance; and the lack of access to healthcare systems during the peaks of the pandemic over the last 3 years.[2] In a recent survey of 155 countries, about 53% of individuals reported a partial or complete reduction of their healthcare access for non-communicable diseases.[9]

Stress hyperglycemia

Stress hyperglycemia is a well-known entity that is commonly observed among patients hospitalized for various surgical and medical conditions. It is an indication of relative insulin deficiency, and is therefore associated with increased lipolysis and free fatty acid circulation.[10]Therefore,these individuals have higher levels of inflammatory markers, and are at higher risk of cytokine storm- which by itself worsens insulin resistance and induces hepatic glucose production through the release of counter-regulatory hormones.[11]Unfortunately, although stress hyperglycemia is a commonly encountered entity, there are only few studies that continued the post-discharge follow up of those patients, which makes it difficult to conclude whether they

eventually develop diabetes or not. Ali Abdelhameed Y et al reported in a meta-analysis of four cohort studies that 131 cases (18.8%) of 698 patients who developed stress hyperglycemia during acute illness persisted to have long-term diabetes after a 3 month follow up period following their recovery. Therefore they concluded that stress hyperglycemia was associated with increased incidence of long-term diabetes with an odd ratio(OR) of 3.48; 95% CI 2.02-5.98. It is worth mentioning, however, that the cut-off points for definition of stress hyperglycemia vary among the studies reviewed.[12]

Direct effect on Pancreas

Viral infections are known to have direct and indirect effect of the pancreas. Pancreatic inflammation is commonly observed in several viral infection, such as measles, cytomegalovirus , mumps , hepatitis and human immunodeficiency virus.[13]Viral infections also may be associated with type I diabetes (T1DM) autoimmunity as is the case with enteroviridae.[3] Increased risk of type II diabetes was also observed among individuals infected with hepatitis C and B viruses in several retrospective and prospective studies.[4,14]infection with Coxsackie B virus cause islet cell functional impairment and increases β-cell apoptosis.[15]

Sars-Cov-2 binds to the angiotensin-converting enzyme 2 (ACE2) receptor which is present in abundance in the pancreatic islet cells among several other tissues in the body.[7] This may theoretically induce β-cell damage and reduced insulin secretion, however data are quite conflicting in this matter, with some single-cell RNA surveys reporting a limited expression of ACE2 in pancreatic islet cells, and a low expression of receptor TMPRSS and the newly discovered NRP1 co-receptor which facilitate viral endocytosis and replication.[11]Data, however , support that the release of proinflammatory cytokines and acute-phase reactants can directly induce damage and inflammation to pancreatic islet cells.[16]

Steroid induced impaired glycemic control

Steroids have been widely used in the management of Covid-19 infected patients, based on the supporting evidence of the RECOVERY trial. Steroids are well known for their diabetogenic effect and may play a detrimental role in the hyperglycemia commonly encountered among hospitalized patients with Covid-19 pneumonia and it's complications.[2]in a meta-analysis of 13 studies conducted by Liu XX et al in 2014, 32.3% of patients treated with steroids developed steroid-induced hyperglycemia, and 18.6% developed diabetes.[17]Steroids may also delay or impair the recovery of damaged pancreatic β-cells.[11]

Post-Covid-19 syndrome(post-acute sequelae of Covid-19) or otherwise "long Covid" is defined by the persistence of symptoms beyond three months after the resolution of the infection. It affects approximately 10% of Covid-19 patients and has variable complex symptoms. Persistent diabetes may be part of this intriguing entity.[2]

Vaccines

Vaccines developed against Covid-19 have been reported to worsen pre-existing diabetes, with some individuals presenting with diabetic emergencies shortly after their vaccination.[18-20]There have been reported cases of pre-diabetes converting to diabetes after vaccination as well.[20]T1DM in an 73 year old Japanese woman has been reported eight weeks after the second dose of her Covid-19 vaccine.[21]This is in theory the result of the production of viral proteins in the recipient which may induce similar effects as the virus itself.

The aim of this study is to demonstrate whether exposure to covid-19 antigen is associated with new onset diabetes, and whether the characteristics of new onset diabetes after being exposed to covid-19 antigen (through recent infection or vaccination) differ from patients with newlydiscovered diabetes who were not exposed to covid-19 antigen(control group).

Materials and methods

This retrospective cross-sectional study was conducted in the endocrinology clinic at King Hussein Medical City in Amman, Jordan, during the period from January 2021 to March 2022. All patients aged 14 and above who were diagnosed with new onset diabetes during this period of time were included. Demographic data were extracted from (electronic medical filing system) with the patients' consent (or their guardian's) . The study was approved by the Royal Medical Services Ethics Committee. Blood samples for fasting plasma glucose, glycated hemoglobin (HBA1c), Insulin level, C-peptide level, anti-glutamic acid decarboxylase antibodies(anti-GAD) and anti-islet cell antibodies were collected after an 8-10 hour overnight fast , and analyzed through Standard biochemical kits (Cobas c 311 Hitachi) following standard procedures at Princess Iman Centre for Laboratory Research and Science Center, KHMC. Anthropometric measures were recorded following standard procedures.[22]

A questionnaire was filled with relevant background information(past medical history, comorbidities, family history, exposure to covid-19 infection including dates, and vaccination against covid-19). A positive Covid-19 infection was defined as a positive Covid-19 polymerase chain reaction test.

All patients with pre-existing diabetes were excluded from the study. Also all patients with very recent infection or vaccination (less than 6 weeks before their presentation) were excluded to avoid any bias that may result from recent metabolic disruption due to acute illness. All included patients were drug naïve at the time of sample withdrawal.

Body mass index was calculated using the formula BMI= weight (kg)/Height2 (m2). Subjects were classified to non-obese: BMI 18.5- 24.9, overweight 25.0-27.5, and obese 27.5-40 kg/m2 . Diabetes was diagnosed according to American Diabetes Association (ADA)13 recommendations as fasting plasma glucose 126mg/dl on two or more occasions and/or HbA1c 6.5%.[23]

The sample was then divided to two groups, Group 1 were the patients with new onset diabetes who had recent exposure to covid-19 antigen through vaccination or infection dating less than 3 months before their presentation , and Group 2 were all the patients with new onset diabetes who were either unexposed to covid-19 antigen, or their exposure dates back to more than 3 months before their presentation with diabetes.

Statistical analysis

SPSS IBM software version 28.0 was applied in our analysis. Categorical data were expressed in frequency and percentage, scale variables were expressed in mean +/- standard deviation (SD), a Chi-square for independence was used to explore association between categorical data. Welch independent t-test was used for mean differences on scale variables in case of homogeneity assumption violation, p value set at <0.05 deemed statistically significant.

Results

Descriptive demographic analysis of the cohort **(Table I).** Anthropometric and clinical indices are shown including means and standard deviations(SD) . 110 patients were enrolled, 82 males, (74.5%), and 28 females(25.45%) . The average age was 37.71 +/- 11.57 years, the mean BMI for the cohort was 28.16 +/- 4.7kg/m^2

61 patients (55.5%) were exposed to covid-19 antigen through vaccination or infection 3 months before the onset of their diabetes or less, hence they were assigned to group 1. 49 patients (44.5%) were either unexposed to covid-19 antigen or their exposure dates back to more than 3 months before the onset of their diabetes. All patients in our cohort who were infected with covid-19 had either mild or moderate disease. Only four of them required steroid treatment for their infection (group 1). None of the patients were on steroids at the time of the sampling. Two patients presented with mild and moderate diabetic ketoacidosis, both were later diagnosed with T1DM based on their C-peptide levels.

Biochemical profile is depicted in **(Table II) .**

The average fasting plasma glucose for Group 1 was higher 344.26 +/- 237.88 mg/dl, compared to Group 2 (312.34 +/- 158.08mg/dl), however it was not statistically significant (p-value of 0.422 which is statistically insignificant).

The average HBA1c for Group 1 was 10.82 % +/- 2.12, and for group 2 10.88% +/- 2.41 (p.value 0.879).

Insulin levels were also comparable in both groups, the average insulin level for group 1 was 10.54 mIU/L +/- 3.8, and for group 2 9.82mIU/L +/- 5.46, with a p-value of 0.36.

C-peptide however was higher among patients recently exposed to covid-19 antigen compared to those who were unexposed or their exposure is relatively older in date, C-peptide for group 1 was 2.97 +/- 1.09 ng/ml, vs 1.94 ng/ml +/- 0.77 for group 2 , with a statistically significant p-value of 0.000. see **(figure 1).**

Only 23 patients (about 37%) from group 1 reported a positive family history of diabetes (mainly T2DM) , whereas in group 2 more than 50% of them had a positive family history of diabetes (28 patients) with a statistically significant p-value of 0.036.

There was no significant difference in the average BMI between the two groups, with the majority of the cohort being overweight or obese.

The presence of comorbidities was more common in group 2 patients, as only 6.6% of group 1 were hypertensive as compared to 14.28%. The presence of hyperlipidemia was almost equal in both groups with an average of 33% and no statistical significance.

TABLE I: DEMOGRAPHIC AND CLINICAL VARIABLES FOR CROSS-SECTIONAL STUDY FOR PEOPLE WITH NEW ONSET DM IN ENDOCRINE CLINIC AT KHMH FROM JAN 2021 TO MARCH 2022,ANTIGEN EXPOSURE >3 MONTHS (GROUP2),ANTIGEN EXPOSURE <3 MONTHS (GROUP 1)

VARIABLES		**OVERALL (110) ∓SD**	**GROUP 2 (49) ∓SD**	**GROUP 1 (61) ∓SD**
AGE (YRS)		37.71 ∓11.57	38.59 ∓ 11.64925	37.01639 ∓ 11.56502
GENDER	*FEMALE*	28(25.45%)	12(24.48%)	16(26.22%)
	MALE	82(74.54%)	37(75.51%)	45(73.77%)
	F: M	1: 2.92	1: 3.083	1: 2.81
BMI		28.16147362 ∓4.70511795	28.042906 ∓ 4.9231331	28.256716∓ 4.5614818
	NORMAL	22(20%)	13(26.53%)	9(14.75%)
	OVERWEIGHT	64(58.18)	26(53.06%)	38(62.29%)
	OBESE	24(21.81%)	10(20.40%)	14(22.95%)
FH	YES	51(46.36%)	28(57.14%)	23(37.70%)
	NO	59(53.63%)	21(42.85%)	38(62.30%)
INFECTION	YES	32(29.09%)	6(12.24%)	26(42.62%)
	NO	78(70.90%)	43(87.75%)	35(57.73%)
VACCINE	YES	105(95.45%)	46(93.87%)	59(96.72%)
	NO	5(4.54%)	3(6.12%)	2(3.27%)
VACCINE TYPE	SPOTNIC	1	0	1
	MODERNA	1	1	0
	ASTRAZENECA	13	11	2
	PFIZER	48	17	31
	SINOVARMSINOFARM	36	17	19
DYSLIPEDEMIA	YES	37(33.63%)	16(43.24%)	21(56.75%)
	NO	73(66.36%)	33(45.20%)	40(54.79%)
HTN	YES	11(10%)	7(14.28%)	4(6.55%)
	NO	99(90%)	42(85.71)	57(93.44)

TABLE II: BIOCHEMICAL VARIABLES FOR CROSS-SECTIONAL STUDY FOR PEOPLE WITH NEW ONSET DM IN ENDOCRINE CLINIC AT KHMH FROM JAN 2021 TO MARCH 2022 ,ANTIGEN EXPOSURE >3 MONTH (GROUP2),ANTIGEN EXPOSURE <3 MONTH (GROUP 1)

VARIABLES	OVERALL (110) ∓SD	GROUP 2 (49) ∓SD	GROUP 1 (61) ∓SD	MEAN DIFF ∓SD OR OD	P-VALUE
FASTING BLOOD SUGER	330.04 ∓205.94	312.35 ∓158.09	344.26 ∓237.89	-31.92∓ 39.60	0.422
HBA1C	10.85 ∓2.25	10.89 ∓2.41	10.82 ∓2.12	0.07 ∓0.43	0.879
INSULIN(2 MISSING)	10.26 ∓ 4.66	9.82 ∓ 5.46	10.65 ∓3.85	-0.83 ∓0.90	0.360
C PEPTIDE (2 MISSING)	2.52 ∓ 1.10	1.94 ∓ 0.78	2.98 ∓ 1.09	-1.03 ∓ 0.19	0.000

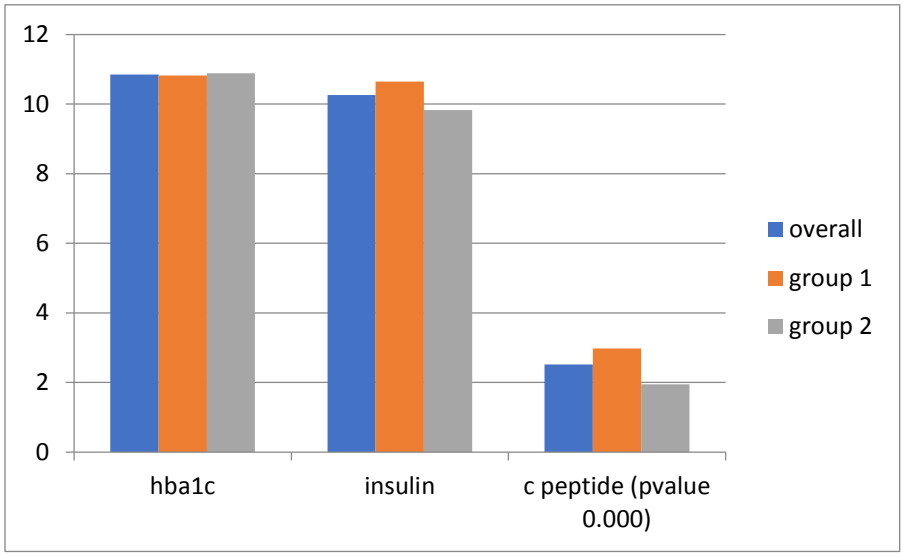

Figure 1: HBA1C,INSULIN, CPEPTIDE LEVELS FOR OVERALL COHORT GROUP 1 AND GROUP 2.

Discussion

This is one of the few studies to assess the association between covid-19 infection and diabetes, and it is the only one relating covid-19 vaccine relation to diabetes.

There have been several studies variably deigned to look into the association between covid-19 infection and new onset diabetes.

Li et al (24) conducted a retrospective observational trial in China including 453 patients with laboratory confirmed SARS-COV-2 infection, and he concluded that 94 patients (21%) were

newly diagnosed with diabetes during their admission. He also concluded that patients with new onset diabetes were at increased risk for Intensive care unit admission and complicated course of the infection.[24]

In a multicenter surveillance study in the US, conducted by Ebekozien et al(25), 6 patients out of 64 had new onset T1DM, 5 of which had recent or ongoing Covid-19 infection.[25]

Sathish et al (26) performed a meta-analysis of 8 studies, involving 3711 covid-19 infected patients, and concluded an estimated prevalence of new onset diabetes of 14.4%.[26]

Yang et al(27) conducted a retrospective cohort study of 69 hospitalized patients with covid-19 and reported a 53.85% prevalence of new onset diabetes among critically infected patients , and a 13.95% among moderate-severely infected patients.[27]

All the previous conducted studies enrolled patients who were actively infected with Covid-19, and there was no long-term follow up of those patients to study the characteristics of their new onset diabetes and whether this was reversible or part of long term sequelae of Covid-19 infection.

Also, apart from few case series and case reports, there have been no trials conducted to demonstrate the potential diabetogenic effect of covid-19 vaccines till the date of writing.

Covid-19 vaccines produce viral particles and therefore can potentially induce similar clinical sequelae as the infection itself. For instance there have been several reports of subacute thyroiditis following Covid-19 mRNA vaccination, which may also follow the infection itself.[28]There are also several reports of thrombotic phenomena and vaccine-induced interstitial lung disease.[29,30]

In our cohort the majority of our patients were males (81 males vs 29 females) however this may be attributed to the fact that our center is a military service, hence the majority were recruits referred from their military units. Also due to lockdown policies there was some limitation to healthcare access at the beginning of our patient enrollment. The global male to female ratio in terms of diabetes is 1.5: 1 respectively, however in a 10 -year diabetes risk forecast in Jordan published in 2016, the majority of the population enrolled were men, forming about 64.9% of the participants.[31] interestingly enough, Sathish et al (26) also reported that all thestudies included in their review analysis had more males than females, with the proportion of males ranging from 53.3 to 80%.[26]

There was no gender predilection as to the risk of developing diabetes after exposure to covid-19 antigen, however.

It is quite challenging to accurately date the onset of diabetes, however in our cohort we depended on past medical records including old data of glycated hemoglobin and fasting plasma glucose. Any patients who had previous evidence of glycemic dysregulation was excluded from our cohort. Also patients were specifically asked about the presence of symptoms of hyperglycemia, if any, and their disease was dated back to the onset of their symptoms regardless of the timeline of their presentation.

We defined recent exposure to covid-19 antigen as any exposure dating less than 3 months prior the onset of their glycemic dysregulation, as it is likely a disorder that appeared during their exposure and continued after the resolution of the insult which may be part of “long Covid” syndrome. Any exposure dating more than months was considered unlikely to be related to exposure.

Group 1 patients had less risk factors for diabetes, as they were less likely to have positive antibodies against islet cells and anti-GAD antibodies. They were also less likely to report a positive family history of diabetes, and less likely to have comorbidities. Group 1 patients had comparable BMI to group 2 patients.

Most of our cohort patients were initially managed with insulin to eliminate glucotoxicity ,[32] and patients who presented with diabetic ketoacidosis and had low C-peptide were treated as T1DM. Unfortunately not all the patients in the cohort have had as yet sufficient follow up to stratify them into either T1DM or T2DM.

Interestingly enough, the average C-peptide in Group 1 patients was significantly higher than Group 2 patients .(2.97 +/- 1.09 ng/ml, vs 1.94 ng/ml +/- 0.77 for group 2 , with a statistically significant p-value of 0.000) .Also the average fasting plasma glucose was higher for Group 1 patients, although the latter showed no statistical significance.

This is in keeping with what has been previously described by Ghosh et al (33) who reported higher C-peptide levels as well as fasting plasma glucose in the group of patients diagnosed with new onset diabetes during Covid-19 pandemic compared to those diagnosed before Covid-19 era. However he did not find statistically significant difference in the new onset diabetes group post-Covid era between those who were infected and those who had negative antibodies. This may in part be because they did not take into account patients who were vaccinated against Covid-19.[33]

Similar biochemical profile has been also described by Montefusco et al (34), who reported elevated mean fasting insulin, proinsulin and C-peptide in patients with Covid-19 as compared to healthy controls. They also concluded that those glycometabolic abnormalities may persist for at least 2 months after their recovery from acute infection.[34]

There have been no conclusive long term prospective studies as yet to follow up patients with new onset diabetes after Covid-19 exposure. Also there is no sufficient data to support a causal relationship between covid-19 and diabetes, and which type of diabetes may be triggered SARS-COV-2. Wander et al (35) conclude in a retrospective cohort study among 2,777,768 subjects using Veterans Health Administration data that SARS-COV-2 was associated with higher risk of incident diabetes among men (odds ratio(OR) 2.56 [95% CI 2.32-2.83], but not women 1.21[0.88-1.68] in a 120 day follow up period.[35]

Limitations

It is quite challenging to point a finger in the timeline of diabetes, so one cannot be certain whether the onset is, for example, actually when patients' symptoms started or by the time the glycated hemoglobin was found to be elevated. We tried to minimize such inaccuracies by looking back into the records for previous normal glucose and HBA1c levels, or by the fact that a large proportion of our cohort are army recruits who are health checked on regular basis.

Also we defined previous Covid-19 infection by means of RTPCR, and this would eliminate all patients who were actually exposed to covid-19 but never did an RTPCR to determine their infection.

Conclusions

In our study, patients who were recently exposed to covid-19 antigen through recent infection or vaccination, had less risk factors predisposing to diabetes and were found to have higher C-peptide than those whose exposure dates more than 3 months before the onset of their diabetes or were unexposed to covid-19 antigen. This may suggest an independent association between Covid-19 exposure and new onset diabetes that persists well after resolution of the infection. In our study there was no evidence of increased autoimmunity in those individuals compared to our control group, as there was no statistical significance in the presence of antibodies in both groups.

Future projections

Further prospective studies should be conducted aiming to shed a light to the characteristics of this new onset diabetes that results after covid-19 exposure, and whether the glycemic dysregulation is permanent or maybe reversible with time. (This is a long paragraph for conclusion)

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