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Asymptomatic COVID-19 among individuals living with diabetes: Rapid scoping review

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Abstract

Background and Aim: There is concern over the novel coronavirus (COVID-19) in individuals with diabetes mellitus. In the ongoing discourse, interest arises *"if medicines we already have are good enough to buy patients more time"* and *whether diabetes drugs are friends or foe.* This study focused on whether oral hypoglycaemic drugs constitute complementary medicine for COVID-19 in those living with diabetes.

Method: Rapid scoping review was done and articles on PubMed and research News related to COVID19 were screened. Focus was outcome of asymptomatic COVID-19 rehabilitative management in people living with diabetes.

Results: From over 14,600 articles, 3 papers were selected and critically appraised. Up to 30% of COVID-19 cases may have diabetes as pre-existing and most will be symptomatic of which about a quarter may aggravate. This prevalence of aggravation is higher than in the subpopulation with only respiratory disease. Among the asymptomatic subpopulation, rehabilitation seems absolutely and most successful in preventing progression to symptomatic status when compared to other COVID-19 subpopulations.

Conclusion: The results signify that some of the medicines already available are good enough to buy COVID-19 patients time. However, majority of COVID-19 cases with pre-existing diabetes could be symptomatic and likely to aggravate. While routine clinical management may be doubling up as complementary medicine for COVID-19, effect may be observable in those without symptoms. Concern on glucocorticoid use is warranted, especially in diabetes clients who are immunocompromised that may worsen with the therapy.

Highlights

- Up to 30% COVID19 cases have pre-existing DM and most are symptomatic. Glucocorticoid is common anti-inflammatory drug used.
- In symptomatic COVID19 cases: aggravation has been recorded among those with diabetes than in respiratory disease.
- In asymptomatic COVID19 cases: best management outcome has been recorded in diabetes subgroup compared to other conditions.
- Antioxidant and immunomodulatory properties of hypoglycaemics may be helping while glucocorticoids have worsening effects.

Introduction

There is concern over the novel coronavirus (COVID-19) among individuals with diabetes mellitus. In the treatment roadmap of COVID-19; there are options including vaccine, anti-inflammatories, management of symptoms and complementary medicine. In the ongoing discourse, interest arises *"if medicines we have are good enough to buy patients more time"* [1].

Specifically for those living with diabetes, there is related interest whether diabetes drugs are friends or foe [2]. Therefore, this study focuses on whether oral hypoglycaemic drugs constitute complementary medicine for COVID-19 in diabetes. This objective is in line with suggestion to investigate outcomes data with regards to the effects of hypoglycaemic drugs [3].

Method

This was a rapid scoping review that followed two processes. The search terms on PubMed were in add-on sequence of COVID-19, diabetes, asymptomatic and treatment with no time bound applied. Additional process was review of research News updates – with vigilance for reports involving asymptomatic COVID-19 comorbidity with diabetes and follow-up evaluations. The main interest was to compare outcome of asymptomatic COVID-19 rehabilitative management in people living with diabetes.

Results

Over 14 600 articles on COVID-19 have been indexed in the searched database, and 3% involved diabetes. However, only 7 papers appeared to include asymptomatic considerations (Table 1), of which 2 were critically reviewed [4,5]; and one delineated those with diabetes who were COVID-19 asymptomatic.

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Key words: *COVID19 pandemic, complementary medicine, diabetes mellitus, hypoglycaemic drugs, management outcomes*

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Table 1. Sequence and outcome of literature search

Steps	Search term	No. of articles
1	COVID19	14602
2	COVID19//diabetes	427
3	COVID19//diabetes//asymptomatic	7
4	COVID19//diabetes//asymptomatic//treatment	2

In the research News updates, one was retrospective evaluation and categorized the diabetes subpopulation into asymptomatic versus non-asymptomatic [6]. Therefore, 3 papers were critical appraised and summary results show that:

Approximately 30% may comprise coexisting DM and a significant minority could be asymptomatic. Besides antimicrobial agents, glucocorticoid is the common anti-inflammatory drug for the COVID-19 [5].

Disease aggravation could be about a quarter (26%) of people living with diabetes. This level of aggravation is high when compared to the subpopulation of those with only pre-existing respiratory disease [4].

Comparing management outcome in those without symptoms (i.e. asymptomatic COVID-19 with diabetes or other pre-existing conditions), rehabilitation may be most successful among the diabetes group (Figure 1) [6].

Considering effect of the management on haematological indices for immune response, further results show average 23% of those who progress have low lymphocyte, platelet and white blood cell counts. Among the subgroup who did not progress, averaged 14% have low counts of the haematological indices (Figure 2).

Discussion

This brief review surmises common phenomenon in research whereby perspectives of observations differ according to objectives and protocols. Here, three different perspectives present a holistic view. First, while COVID-19 patients may have pre-existing diabetes, glucocorticoid may also be used in the treatment. This is important because of the hyperglycaemic and immunosuppression side-effects of glucocorticoids. Arguably, glucocorticoids should be contraindicated in immunocompromised COVID-19 patients [7,8]. This contraindication may be relevant in diabetes and geriatrics [3,9], especially considering the glucocorticoids side-effects of worsening both hyperglycaemia and immunosuppression.

Secondly, disease aggravation appears to be in a smaller fraction of the diabetes subpopulation. While this is subject to validation, it is pertinent to note that such aggravation is less in the subpopulation with pre-existing respiratory disease. Third and more striking is where the COVID-19 asymptomatic cases were assessed that none of those with diabetes progressed to symptomatic status of the respiratory infection (Figure 1).

We previously reported on a family case of metabolic syndrome [10], and one family member died of disseminated intravascular coagulation (DIC) complication in 2018. In the ongoing COVID-19 pandemic, a recent report has indicated DIC as the complication underlying the deaths [11]. Therefore, this has drawn our interest on relevant interaction in COVID-19-diabetes comorbidity. It suffices to note that the interaction can be in the pathophysiological processes as well as by drug-health interaction.

In terms of pathophysiology, oxidative stress is involved in diabetes and athero-thrombogenic process [12,13]. Hence there is application of antioxidant micronutrients in diabetes management [14]. Mitochondria damage is involved in several diseases and includes mitochondrial ROS production in platelets, which constitutes part of risk of DIC [15]. Thus, a pre-existing disease such as diabetes can exacerbate athero-thrombogenesis *en-route* formation of DIC. In this report, results indicate that coronavirus disease may be aggravated more in diabetics than in those without diabetes. What this report contribute to the ongoing discourse is a reminder albeit what is already known that oxidative stress damage leading to DIC is probably exacerbated in COVID-19 comorbidity with diabetes.

In terms of treatment interactions: Antioxidants have immunomodulatory effect [16]; and have been applicable in diabetes management. Antioxidants remove free radicals to reduce DIC formation process [17]. For instance, metformin has been discussed and evaluated for antioxidant and immunomodulatory functions. In terms of the COVID-19 pandemic, it is necessary to re-articulate how diabetes drugs with antioxidant *cum* immunomodulatory properties can be appropriated in management of COVID-19 patients with diabetes.

The relevance of this discourse is important with regard to *"if medicines we already have are good enough to buy patients more time" [1]; and whether diabetes drugs are friends or foe [2]*. In regard to the study report reviewed and graphically re-presented (Figure 1), the non-progression of asymptomatic COVID-19 infected individuals living with diabetes can only be attributed to their hypoglycaemia management. This notion is supported by the potential of antioxidant and immunomodulatory effects of hypoglycaemic drugs including metformin [18,19].

This review makes a point that symptomatic people with COVID-19 who have diabetes are more likely to progress to severe stages due to complex pathophysiological processes including but

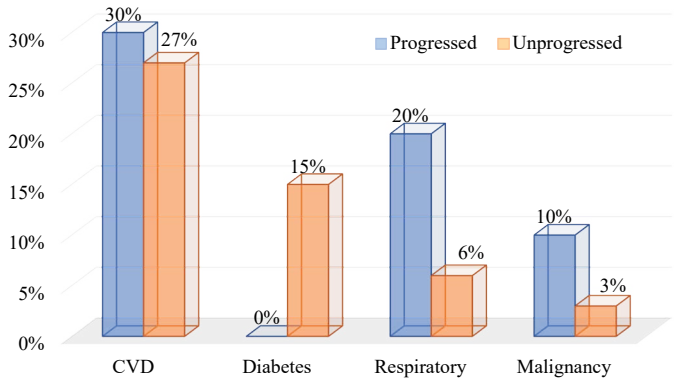

Figure 1. Clinical characteristics of 43 asymptomatic COVID19 patients on follow-up

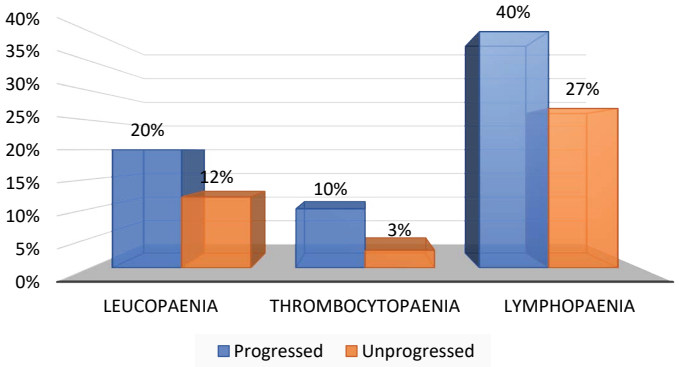

Figure 2. Effects of management on haematological indices of immune response

not limited to aggravated immunosuppression possibly arising from side-effects of anti-inflammatory drugs that may worsen both glycaemic control and immune status. On the other hand, asymptomatic people with COVID-19 who have diabetes are less likely to aggravate. Possible reason is that in the absence of polypharmacy, the role of antihyperglycemic therapy may include antioxidant *cum* immunomodulatory properties.

From the clinical laboratory perspective, there is no gain saying the fact that routing full blood count constitute a valid tool for assessment. In the case reviewed, reported data show comparison of the subgroup who progressed relative to the non-progressed – re: abnormally low counts are more in the progressed group (Figure 2). It may also benefit to note that the risk of DIC can be assessed by whole blood viscosity using routine haematocrit and serum protein tests [20], which are available in most pathology services.

To conclude, this rapid review submits that some of the medicines already available are good and effectively 'buying patients more time'. The treatment outcomes of diabetes drugs may be more evident in the asymptomatic COVID19 patients. However, the majority of cases with pre-existing diabetes may be symptomatic and likely to aggravate.

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