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Review Article

The molecular pathology at Work: Metformin and Variability in Glycemic Control

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ABSTRACT

Optimized management of type-2 diabetes mellitus (T2DM) remains a challenge not just because micro and microangiopathies', chronic kidney disease, and infections related to poor cellular immunity. Methodology to manage T2DM remains in need for evolution to curb disease and help manage economy of diabetes care. Metformin remains the frontline soldier against T2DM. However, optimized and evidence-based use of metform for managing T2DM in clinics needs better molecular analytics to micro-precise medical management. We evaluated 353 manuscripts to finally shortlisted 45 reviews and RCTs using PRISMA guidelines from Google Scholar, PubMed and Cochrane Reviews. This systematic review attempted to identify the role of pharmacokinetic, pharmacogenomic, epigenetic and mitochondrial factors which can lead to sub-optimal diabetes management, metformin resistance and mutations which could lead to poor to no response to medicine. The most common mutations and polymorphisms in solute channels were observed to reduce the therapeutic efficacy/resistance to metformin efficacy were (Organic Cation Transporter-1-3) followed by (Ataxia Telangiectasia Mutated), (phosphatidylethanolamine N-methyltransferase), (Multidrug and toxic compound extrusion) However various epigenetic factors and mitochondrial genetics factors were also related with suboptimal response to metformin and metabolic complications including lactic acidosis. Finally, we believe more research at national and international level is needed to define the wholesome utility of metformin with understanding about the genetic contraindications to metformin prescription.

Keywords: Metformin, Metformin resistance, metformin response variability, pharmacokinetics of metformin, pharmacogenetics of metformin, Type 2 Diabetes Mellitus.

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INTRODUCTION

Type-2 Diabetes Mellitus (T2DM), has emerge as a challenge in the complex molecular landscape of medicine to manage personalized evidence based therapeutic solutions.[1] Current medical therapies though expanded with options including "Sodium-glucose co-transporter-2 (SGLT-2) inhibitors" and Glucagon Like Peptide-1 (GLP-1) agonist", still rely heavily upon metformin as first line treatment.[2,3] We do realize that T2DM as heterogeneous metabolic disorder with varying pathogenesis needing molecular and nano level signaling pathway alterations to address inter and intra individual clinical outcomes.[4,5] Newer and next-generational scientific data powered by molecular techniques from PCR methods, genotyping and sequencing have dissected out the underlying T2DM biomechanisms at work along with discovering the pharmacogenomics compatibilities between host and drug.[6,7]

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Innovative diabetes model of care though more cost-consuming and requiring newer lab tools with molecular platforms to study T2DM, the futuristic physicians will be needing the concept of "personalized and evidence based medical practice". Timely translation into individualized tailor-made therapeutics without non-desirables effects remains the central dogma of life.[8] Newer evidence now frequently refers to terms related to subjects taking metformin as "Responders" and "Non-responders" identifying patients who somehow could not do well on a specific anti-diabetic therapy or faced a side effects.[9,10] With science now exploring the little genetic defects in diabetic patients making them slightly different in terms of therapeutic response and off-target effects thus highlighting a broad-spectrum but focused approach towards each diabetic patient.

There is more new data on the horizon which has been regularly challenging hyperglycemia variabilities during management by metformin T2DM. However, the data on the subject remains preliminary and challenging in terms of predicting dosage and response among our ever-growing diabetes po-pulation. Intriguing here is the convention that metformin

response variability is not even conceived by many of the general practitioners and patients are to live with metformin use for decades without man-aging hyper-glycemia, micro or macro vascular complications.[11] Furthermore, we are heading fast towards learning the core defective genetics underlying T2DM to subclassify the diabetes into multiple clusters.[12] This quality data on possible sub types/clusters of T2DM phenotype raises a first liner query i.e., "Is metformin a first line anti-diabetes medication for all sub types of T2DM? Probably, the reply will be in the negative. However, the current stan-dard of care in managing T2DM remains "metformin" in the absence of any specified contraindications, which remain affected by multiple genetic and non-genetic factors Figure-1.

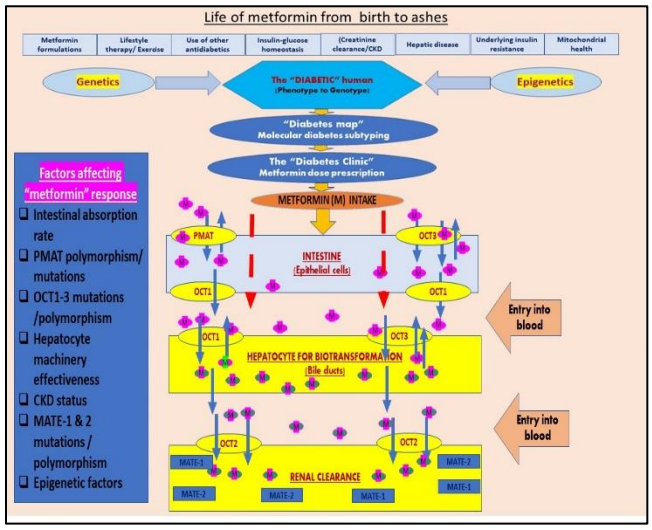


Figure-1: Overview of Metformin Pharmacokinetics and Pharmacogenetics with Overall Pathway and Proteins.

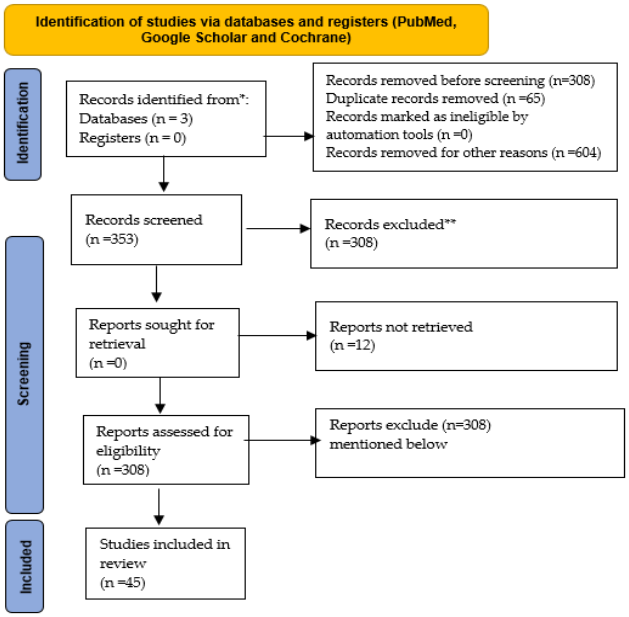
Observational researchers have explored multiple intra-individual pharmacokinetic and pharma-cogenetic variabilities, we do learn that personalized therapy in care remains central to solutions. With this background our research team reviewed existing data on metformin response rate/resistance with objective to develop a systematic review to predict and guide metformin dosing among diabetes patient.

RESEARCH METHODOLOGY.

This systematic review was conducted at the Armed Forces Institute of Pathalogy from September 2023 to March 2024. Ethical approval in this regard was approved via ltr no. CHP-4/READ-IRB/24/2414-25-Mar-2024. Preferred Re-porting Items for Systematic Reviews and meta-analysis (PRISMA) guidelines were adopted for data mining from major search engines including PubMed, Google Scholar and Cochrane reviews. The systematic data research was initiated through aforementioned search engines to include only randomized control trials, previously conducted systematic reviews and reviews in the past 10 years. Observational studies, personal narratives, editorials were excluded from the literature search.

Table-I: Details of Search Engines Explored, key Search Words, Total Articles Selected, Excluded and Finally Included

Ser	Search term	N	Excluded	Included
PubMed/Google Scholar/Cochrane Reviews				
A.	Metformin responders and metformin non-responders	4	4	0
B.	Metformin non-responders	7	7	0
C.	Metformin response rate	97	88	9
D.	Mutations and metformin	87	80	7
E.	polymorphism and metformin	64	50	14
F.	metformin resistance in type 2 diabetes	94	79	15
	Total studies (N)	353	308	45



PRISMA 2020 flow Diagram for new Systematic Reviews which Included Searches of Databases and Registers only

**No automated tools were used*

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

RESULTS

e finally selected 45 manuscripts including RCTs and Reviews using PubMed, Google Scholar and Cochrane Reviews. Major exclusions from systematic research included metformin in non-diabetes conditions (Cancers, PCOS, gestational diabetes, rare diabetes syndromes), combined use with non-metformin therapies, neurological diseases, use of metformin in non-T2DM, articles without full-text, articles in any language other than English, not specifically addressing metformin response, observational studies, comparing metformin within other anti-diabetic medications. Results summary is shown in Table-II.

DISCUSSION

T2DM is a heterogenous disease with included risk associates as micro and macro angiopathies in early phase and later involving all bodily systems. Though growth of knowledge has adopted supersonic pace, handling and unifying new exploratory data in a presentable way also seems to be more daunting tasks. Experts are already foreseeing a broader classification encompassing both genetics, mitochondrial respiratory chain defects and epigenetics and possibly some yet to find newer dimensions to one of the emerfing menace of our civilizations.[9,23,14,39] The research challenge is still on with onslaught of molecular data and development

Table-II: Research output summary for metformin response rate(n=45)

Ser	Key outcomes	Research Category	Research type	Conclusion	Ref
1.	Metformin Associated Lactic acidosis (MALA) reduced from 1960 (50%) to 2014 (25%) [n=20 and n=895]	Review	Pharmacovigilance Study	MALA associated mortality rate dropped from 50% to 25%	Kajbaf et al.13
2.	Organic Cation Transporter (OCT) genes plays a major role in metformin pharmacokinetic response rate (n=30)	Meta-analysis	Pharmacogenomic Study	SLC22A1 (rs622342 and rs628031) polymorphisms were related with metformin response rate	Peng et al.14
3.	Metformin affects hepatic gluconeogenesis in both AMPK dependent and independent manner	Review	Pharmacogenomic Study	Various mutations/polymorphisms define the rate of metformin response including PEPCK and G6Pase	Zhang et al.15
4.	Anti-psychotic induced weight gain management was assessed through 21 RCTs	Meta-Analysis	Pharmacokinetic Study	Intra-individual and inter-individual factors including dosage and associated precautionary defines metformin response rate	Chen et al.16
5.	The TriMaster study (A triple cross-over study) did not use metformin during trial	RCT	Pharmacokinetic study	Highlighted the need for initiating therapy based upon GFR and initial weight to avoid off-target effects	Shield et al.17
6.	Patient -centered genetically evident therapeutic approaches needed for T2DM	Review	Pharmacogenomic Study	AMP-activated protein kinase (AMPK) affect metformin response variability	Guo et al.18
7.	Population wise genetic differences exist in managing T2DM via metformin	RCT	Pharmacogenomic study	The relationship between eGFR and metformin dosage remains variable	Zhang et al.19
8	SLC22A1 variants show less reduction in visceral fat in comparison to WT SLC22A1	RCT	Pharmacogenomic study	Pharmacogenomics plays an integral part in visceral fat deposition and thus indirectly affects metformin response	Sam et al.20
9.	Metformin + insulin in comparison to insulin alone caused drop in Orthostatic blood pressure and worsening of cardiovascular autonomic neuropathy	RCT	Pharmacokinetic study	Metformin can cause worsening of neuropathies	Hansen *et al.*[21]
10.	Highlights patient sub groups, therapy targets and identify possible disease severity	Review	Pharmacogenomic study	Identify specific genetic targets for metformin response i.e., intolerance due to OCT1 variants and SLC2A2 variants	Pearson et al. 22
11.	Identify rQTL and vQTL for T2DM for tracing G×G and G×E	RCT	Pharmacogenomic study	This study provides genetic modelling to assess the combined effects of genetics and epigenetic factors	Maxwell et al.23
12.	Genetic defects in ATM and MATE1 are associated with glycemia management	RCT	Pharmacogenomic study	rs11212617 (ATM) and rs2289669 (MATE1) were significantly affect plasma metformin concentration.	Out et al.24
13.	The association between mitochondrial dysfunction and lactic acidosis hints towards mitochondrial dysfunction	Review	Pharmacogenomic study (Animal Model)	Mitochondrial cytochrome c oxidase (COX) has been shown to relates with Glucose-induced insulin secretion (GSIS), thus signifying the possibility of mitochondrial involvement	Weksler-Zangen et al.25
14.	TODAY (treatment options for type 2 diabetes in adolescents and youth meant to compare T2DM with MODY genetics	Review	Pharmacogenomic study	426 genetic loci were associated with T2DM which were compared with MODY genetics	Arslanian et al.26
15.	ASD youth wit weight gain were evaluated for metformin response genes: ATM, SLC2A2, MATE1, MATE2, and OCT1	RCT	Pharmacogenomic study	Only ATM and OCT1 demonstrated significant genotype impact on BMI	Garfunkel.27
16.	Genetic polymorphism in organic transporter efficiency affect glucose lowering effect of metformin	Review	Pharmacogenomic study	OCT1 and OCT2 mainly affect the glucose-lowering effectiveness of metformin	Li et al.28
17.	Pharmacokinetic effect of metformin multiple metabolic steps	Review	Pharmacokinetic study	SLC2A2, GLUT2, MATE1, MATE2, , PMAT OCTN1are involved in final metformin response rate	Liang et al.29
18.	GoDARTS study not only attempted to predict heritable reduction in HbA1c but identified various levels protein mutations at work to sub-optimize metformin response	Review	Pharmacogenomic study	Step wise role of PMAT, OCT1-3, SLC2A2 and MATE has been identified in net outcome of metformin response	Florez et al.30
19.	Various solute carriers affect metformin response and thus variability in response	Review	Pharmacogenomic study	Genetic polymorphism in SLC22A1(OCT1) affects metformin response	Pradanaet al.31
20.	Measuring impact of pharmacogenomics on metabolic profile in T2DM	Review	Pharmacogenomic study	OCT1, OCTN1, PMAT, SERT, THTR2, MATE 1&2 and others defining metformin response rate	Damanhouri et al.31
21.	Multiple OCTs and drug transporters are involved in "ADME" of metformin.	Review	Pharmacogenomic study	Authors focused on the role of OCTs during absorption, distribution, metabolism and elimination	Chan et al.32

22.	Epigenetic study: Epigenetic triggers in T2DM play a significant role in pathogenesis of T2DM.	Review	Pharmacogenomic study	The epigenetic alterations incorporate short and long Non-coding RNAs and modifications in histones and DNA methylation have a role in pathogenesis of T2DM.	Giordo et al.32
23.	35% response inter-individual variability has been observed across different ethnicities	Review	Pharmacogenomic study	A total of 34 OCT1 polymorphisms identified in 10 ethnic population groups varing response to metformin	Mofo et al.33
24.	Multiple susceptible genetic loci have been identified in managing metformin response	Review	Pharmacogenomic study	Details shared as: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7555942/table/ijms-21-06842-t004/?report=objectonly. Accessed 7/Apr/2024.	Nasykhova et al.34
25.	ACCORD study: Explored some common variants associated with metformin response	RCT	Pharmacogenomic study	Genetic mutation or polymorphism PRPF31, STAT3 and CPA6 associated with metformin response	Rotroff et al.35
26	Authors explored both epigenetic and genetic factors allowing variability in metformin response	Review	Pharmacogenomic study	OCTare affected by both genetic polymorphisms/mutations and epigenetic changes	Kölz et al.36
27	Researchers here have attempted to share multiple genetic targets for different diabetes subtypes	Review	Pharmacogenomic study	Pertinent associations with T2DM response and metformin use were associated with SLC22A1, SLC47A1, ATM, SLC47A1 and TCF7L2.	Florez et al.37
28	18 x articles were reviewed to conclude multiple step-wise constitutional map for defining the heterogeneity of T2DM in terms of side effects and response to metformin therapy.	Review	Pharmacogenomic study	Key identifiers from this reviewed data identified Carriers with reduced functioning of OCT1, PMAT and SERT.	Bave et al.38
29.	Precision medicine in T2DM using pharmacogenomic tools	Review	Pharmacogenomic study	Variable rate of function due to polymorphism/mutations is primarily led by SLCs and AMPK genetics	Khatamier al.39
30.	Detailed review on pharmacological function of metformin in lowering hyperglycemia suggests multi-targeting by variable genetic factors	Review	Pharmacogenomic study	SLC22A, SLC29A4 in OCT1 seem to be key drivers in variable pharamgenomic response in T2DM	Singh et al.40
31.	Role of FGF21 on insulin resistance	Review	Pharmacokinetic study	Metformin reduces Inflammation and stimulate FGF21 to reduce insulin resistance and glucose homeostasis	Al-Kuraish et al.41
32	Metformin responsive in preclinical set ups	Review	Pharmacokinetic study	Metformin is responsive	Zhou et al.42
33.	Role of epigenetics in T2DM complications	Review	Pharmacokinetic study	Epigenetics associates micro-and macrovascular complications thus reducing efficacy of conventional use of metformin	Mannar et al.43
34.	Resistance to metformin to T2DM has rarely been documented	Review	Pharmacokinetic study	Metformin resistance has been observed in managing T2DM	Scheen et al.44
35.	Comparison of multiple hypoglycemic medications	Review	Pharmacokinetic study	Metformin has more pros than cons in managing T2DM and low cost	Sciannimanico et al.45
36	Comparative analysis of using glargine followed by metformin in managing outcomes in youth	RCT	Comparative-cross sectional	IGTT2DM in youth not halt after 3-momths of glargine followed by 9-month of metformin did not showed improved in outcomes	RISE CONSORTIUM.46
37.	Discussed metabolic effects of metformin upon different tissues	Review	Pharmacokinetic study	Though positive effects of metformin, the evidence on positive effects of metformin remain inconclusive	Adeva-Andany et al.47
38.	Assessment of metformin effect on Central nervous tissues	Review	Pharmacokinetic study	There is limited evidence about effects of metformin forhaving positive effects on brain functionality	Cao et al48
39.	Evaluating AMPK driven effects of metformin on inflammation	Review	Pharmacokinetic study	Effects of inhibiting mitochondrial respiratory chain complex 1 and (AMPK) activation	Khodaddadi et al.49
40.	SHIP2 inhibitors are emerging as specified medication therapy for T2DM	Review	Pharmacodynamic study	SHIP2 inhibitors regulates PI3K-mediated insulin signaling	Lehtonen et al.50
41	OCT1 mutations/SNPs have been described to worsen metformin tolerance	Review	Pharmacokinetic Study	Metformin intolerance is associated with reduced functionality im OCT1 variants	Pearson et al.51
42	Epigenetic study: role of miRNAs in metformin tolerance	Review	Pharmacodynamic study	Metformin may alter miRs via AMPK-dependen/AMPK-independent mechanisms	Alimoradi et al.52
43.	Epigenetic study: Role of lncRNAs in T2DM	Review	Pharmacodynamic Study	Metformin regulated lncRNAs in T2DM by altering glycemic pathways	Chang et al.53
44.	Proteomics study "Copenhagen Insulin and Metformin Therapy (CIMT) trial": Plasma (proteins) metabolites altered in T2DM and thus therapeutic response	RCT	Proteomics Study	Metformin treatment is associated with low levels of tyrosine, valine, carnitine along with certain other proteins which are allows identification of HbA1c lowering effect	Safai et al.54
45.	Proteomics study "The CAMERA study": Deals with effects of metformin treatment on various circulating amino acids alterations in blood	RCT	Proteomics Study	Metformin treatment results in sustained and specified changes in aromatic amino acid and alanine	Preiss et al.55

of innovative therapies. The first and foremost approach remains to define the suboptimal response to metformin, where preliminary data suggests failure to achieve/maintain HbA1c <7% within 18 months of regular use metformin or needing an additional glucose lowering medication for managing diabetic hyperglycemia.

Multiple pharmacokinetic and pharmacogenetic factors mostly shape the landscape for any optimized therapeutic within a biological being as highlighted from aforementioned research.[24,29,38] Metformin is no different scenario except the door openers (Solute channels), pathway facilitators and final functional performers differ in terms of "ADME" and pharmacogenomic response rate.[15,19,34] The literature search identifies volumes of data defining variabilities in metformin response among humans either related to pharmacokinetics (ADME) or pharmacogenomic

factors affecting response rates / sensitivity to metformin theray.[32,21,34] The former factor while well-understood still needs optimized management within diabetic care clinics, while the later including "pharmacogenomics of metformin" has also been elucidated in details in recent times. Figure-1 attempts to conclude the different pathways creating obstacles for desirable response without well-documented side effects. There is very limited data dealing metformin response for T2DM within Pakistani population. The review of "PakMediNet" could not identify any specific study assessing metformin resistance or response rate. However, Rashid *et al* from Jinnah Allama Iqbal Institute of Diabetes and Endocrinology (JAIDE) up to 40% metformin non-responders in T2DM participants highlighted a non-Responder rate to be up to 200 (40.5%) in an observational study.[55] However, another study Pakistani population by Moeez *et al* evaluated role of epigenetic biomarker miRNA147 identified the expression to be decreased in metformin non-responders.[56]

A T2DM patient once diagnosed is currently destined to get initiated inevitably with biguanides, mainly metformin as per current recommendations. The second add on therapy is usually added without being consideration about genetic resistance or consideration of any pharmacokinetics alteration to metformin leading not only to suboptimal usage of the wonder drug "metformin" but also the need has actually emerged to establish the pharmacogenomic of metformin utility through pharmacogenomic analysis. At the time of writing the practice guidelines actually do not take into consideration even the possibility of "metformin resistance" nor the resistance or sub-optimal response definitions have been es-tablished/practiced in real-time. However, there is literature which is supporting prior genetic test to learn more about metformin response via genetic test.[32] This conceptual proof of genetic testing for various metabolic and non-metabolic analytics is evolving and likely to prevail in coming times. Goswami *et al* has also discussed the role of genetic testing for metformin.[57] The science of genomics and molecular pathology techniques being revolutionized in 360º and we believe the future must entertain requisite genetic pharma-cok-inetic and pharmacogenomic factors into physician's knowledge-base to define metformin non-responders optimally and indicate requisite testing after necessary consultation with molecular pathologist. Furthermore, Pakistan remains in first 10 countries in terms of diabetes prevalence and met-formin for life with add-ons without evidence may not lead to greater good but harm in terms of lactic acidosis, diabetic complication and extend the economy of care.

We must acknowledge certain limitations to our study: Firstly, we believe their extreme dearth of data within our country with mounting T2DM load, so genetic studies are the need of the time. Therefore, most data shared ushers in from Western hemispheres or non-Pakistani population. Furthermore, there have been other data bases including Encyclopedia of Life Sciences, Web of Science, EMBASE, Scopus, Chinese Medical Current Content (CMCC) and possibly others. However, a single Centre study could not have covered all.

This review has significant clinical importance from the point of a 3rd world country where T2DM has plagued in every possible way. We believe this is the primary "systematic review" on metformin response rate in T2DM from Pakistan encompassing pharmacogenetic, pharmacokinetic and proteomic data relating to variability/resistance to therapy. Within country positioning itself as third on victory stand, we MUST emphasize timely, focused and emergent steps to root-out the emerging menace before the tsunami of diabetic complications take over our healthcare systems. Linked directly to the diabetic patient burden is "cost of care" for a struggling economy, which may consume billions in USD along with sickness take an indirect toll by loosing productive life year loss. Another aspect of this to create our genomic data base to synthesize our region-specific guidelines in wholesome with interventions being initiated in early life years. We finally believe that our primary review work, though preliminary from our perspective must be strengthened by more quality research and developing timely interventions.

CONCLUSION

We feel pharmacokinetic, genetic and epigenetic factors must be included in a diabetic patient's work up. There is also a need to evaluate the incorporation of right-sized genetic diagnostic arsenals in our fight tor preventing, treating and curing T2DM from our country. Physicians, laboratorians and public health experts must join hand to define a cost-effective but appropriate molecular diagnostic strategy for this life-time associate wherever indicated.

Conflict of Interest: None.

DECLARATIONS

Author's contribution

Author-1: Corresponding author, research plan, plan execution via tasking, contribution to critical writing, systematic review,

Author-2: Idea conception, research plan, plan execution via tasking, contribution to critical writing.

Author-3: Research plan execution, discussion writing and methodology, systematic review, contribution to critical writing,

Author-4: Systematic review, contribution to write up.

Author-5: Systematic review, contribution to write up,

Author-6: Review, contribution to write up, proof reading.

Author-7: Review, contribution to write up, proof reading,

Author-8: Contribution to research, write up, proof reading

Author-9: Review, contribution to write up, proof reading. All authors provide significant contributions.

All authors provide significant contributions.

Consent for publication: Not applicable, review article (No individual data was presented)

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