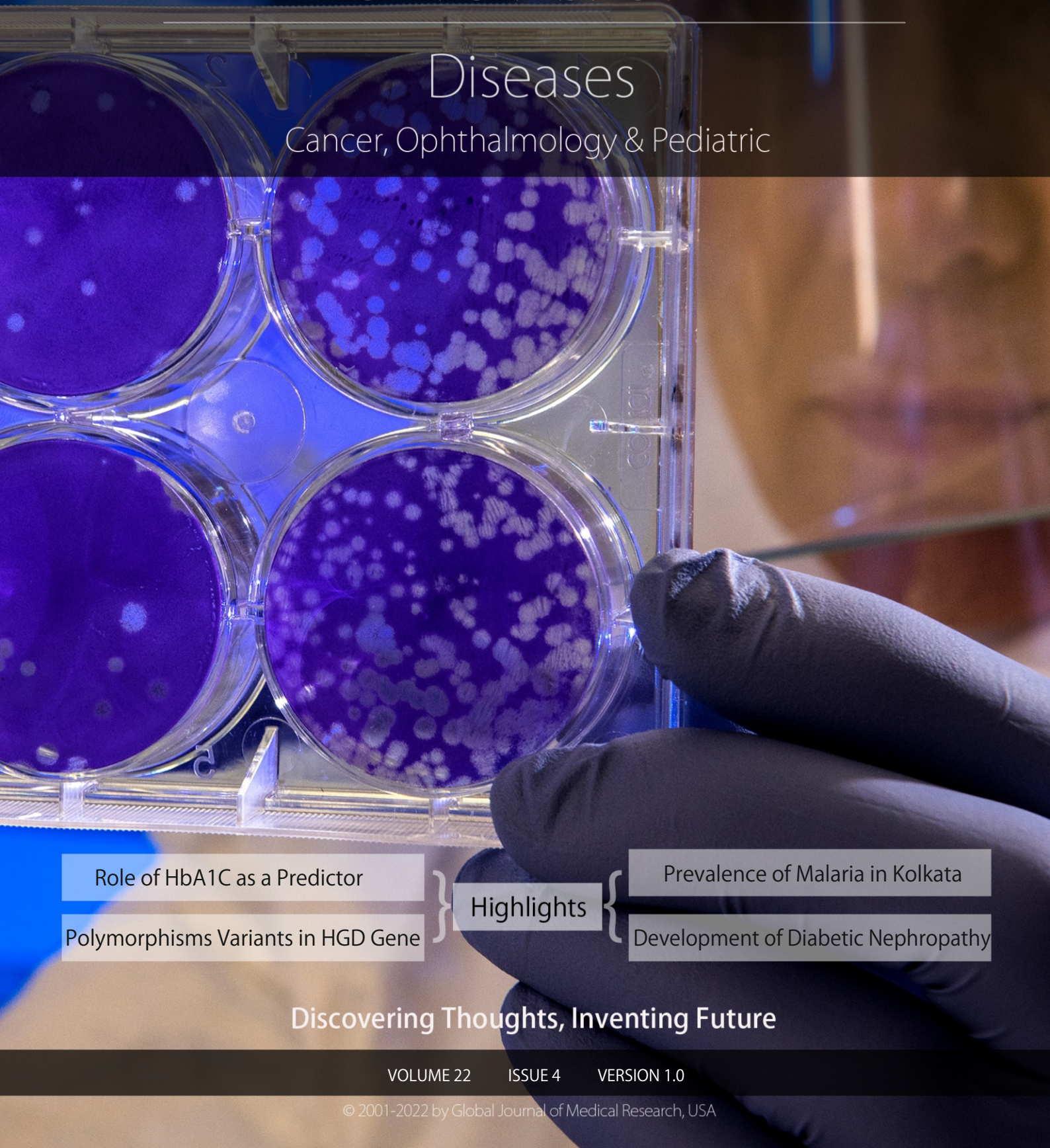
Online ISSN : 2249-4618
Print ISSN : 0975-5888
DOI : 10.17406/GJMRA

Global Journal

of Medical Research: F

Diseases

Cancer, Ophthalmology & Pediatric



Role of HbA1C as a Predictor

Polymorphisms Variants in HGD Gene

Highlights

Prevalence of Malaria in Kolkata

Development of Diabetic Nephropathy

Discovering Thoughts, Inventing Future

VOLUME 22 ISSUE 4 VERSION 1.0

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Volume 22 Issue 4 (Ver. 1.0)

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Contents of the Issue

Global Journal of Medical Research: F
Diseases
Volume 22 Issue 4 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Epicapsular Stars: A Rare Entity

By Fiqhi Aissam

Hospital Militaire Rabat Maroc

Introduction- An 18-year-old female presented to the ophthalmology clinic for allergic conjunctivitis with a 20/20 best-corrected visual acuity. Slit-lamp examination of her left eye revealed, fortuitously, multiple tiny, stellate-shaped, pigment deposits on the anterior lens capsule suggestive of Epicapsular stars. These pigmentations were clustered in an exceptional shape reminiscent of the letters "J" and "Y". Epicapsular stars result from incomplete apoptosis of the anterior portion of ''tunica vasculosa lentis''. They could affect one or both eyes, be isolated or clustered, and are usually asymptomatic like in our case. Consequently, our patient didn't need any treatment but has still followed up regularly.

GJMR-F Classification: DDC Code: 617.7 LCC Code: RE1

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Fiqhi Aissam

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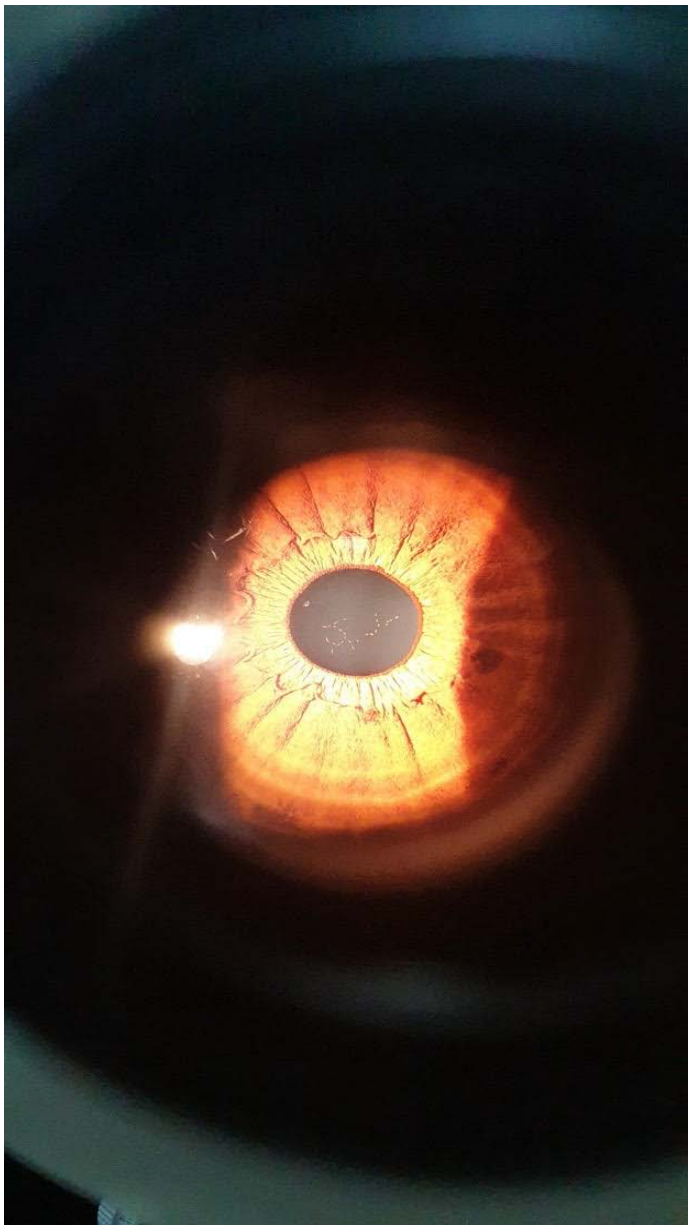

Figure 1: Pigmentations clustered in an exceptional shape reminiscent of the letters "J" and "Y"

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Global Journal of Medical Research: F
Diseases
Volume 22 Issue 4 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
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To Evaluate the Role of HbA1C as a Predictor for the Development of Diabetic Nephropathy in Type 1 Diabetic Patients

By Dr. Sushant Duddala, Arghadip Das, Shaibesh M Shrestha, Dr. Snigdha Shanti Cheela, Dr. Himani J Suthar, Dr. Vinodh Boopalraj & Irshan Ali Mohammed

Abstract- *Aim:* The aim of this study to evaluate the role of HbA1C as a predictor for the development of diabetic nephropathy in type 1 diabetic patients.

Methods: This prospective observational study was carried out by involving 120 patients. The ‘‘fluctuations” in HbA1C over time was assessed. HbA1C fluctuation was defined as an increase in HbA1C of more than 2% between two consecutive measurements, or an increase of more than 1% at 2 points in time.

Results: There was no association between gender and the development of diabetic nephropathy ($p = 0.95$). There were no significant group differences in the ‘‘age at onset of diabetes” or ‘‘time period from the onset of diabetes till admission to the chronic care center” ($p = 0.48$ and $p = 0.81$, respectively). The association between fluctuations in HbA1C and diabetic nephropathy is shown in Table 1.

Keywords: *type 1 diabetic, diabetic nephropathy, glycosylated hemoglobin (HbA1C).*

GJMR-F Classification: *DDC Code: 616.61071 LCC Code: RC918.D53*

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Conclusion: We concluded that the T1D patients who have a similar mean HbA1C may progressively behave differently in terms of developing nephropathy, depending on the fluctuations in HbA1C.

Keywords: type 1 diabetic, diabetic nephropathy, glycosylated hemoglobin (HbA1C).

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I. Introduction

The proportion of patients with end-stage renal disease (ESRD) caused by diabetes has progressively increased during the last few decades and diabetic nephropathy (DN) is the leading cause of end stage renal disease (ESRD) in the world. Diabetic nephropathy is defined by persistent albuminuria, declining glomerular filtration rate (GFR) and progressive rise in blood pressure. Approximately 40-50% of patients with type 1 diabetes and 20-30% of patients with type 2 diabetes develop diabetic nephropathy.[1] Based on studies in type 1 diabetes, it had been generally considered that once overt diabetic nephropathy, manifesting as persistent proteinuria, is present, it was only possible to slow, but not halt, the progression toward ESRD.[2-4] This led investigators during the early 1980s to search for early predictors of diabetic nephropathy. Most investigators now agree that diabetic nephropathy result from the interaction of multiple metabolic, genetic and other factors of which chronic hyperglycemia is one of the most significant factor in both the initiation and progression of the disease.[5] Different randomized controlled trials and observational studies have strongly suggest that hyperglycaemia or closely associated factors of poor glycaemic control, like HbA1c is a good predictor of diabetic nephropathy[5-9], and is highly correlated with fasting blood glucose (FBG) and does not require measurement in the fasting state.[10] One study showed that increasing HbA1c categories had a higher prevalence of chronic kidney disease (CKD) and micro or macro-albuminuria. In the multivariable models, HbA1c categories above 7.0% were significantly associated with increased prevalence of diabetic nephropathy compared with the lowest category.[11] Another study demonstrated that HbA1c >6.5% predicts a future risk of kidney disease. Above the threshold point with the increasing of HbA1c levels the risk of kidney diseases also increases sequentially.[12] It indicates that HbA1c may be used as a useful marker for nephropathy along with other risk factors. The ADVANCE trial documented that (in subjects with type 2 diabetes mellitus) strict glycaemic control (mean HbA1c: 6.5%) in comparison with standard control

(mean HbA1c: 7.3%) is associated with a significant reduction in renal events, including onset of or worsening of nephropathy [hazard ratio (HR) 0.79; P = 0.006], new-onset microalbuminuria (HR 0.91; P = 0.02), and, in particular, development of macro-albuminuria (HR 0.70; P <0.001).[13] There are several other predictors[14-18] of diabetic nephropathy including advanced age, longer duration of diabetes, body weight, smoking, diabetic ketoacidosis, mild to moderate nonproliferative diabetic retinopathy, proliferative diabetic retinopathy (the most prevalent predictor), proteinuria, hypertension, dyslipidaemia, physical inactivity etc. Both sexes are vulnerable to diabetic nephropathy, although there is an unexplained male preponderance of diabetic nephropathy. Ethnicity and family history also affect the risk of diabetic nephropathy. The burden of nephropathy will increase in future as the incidence of diabetes increases and the age of onset declines, although the effects may be lessened by the use of emerging therapies.[19] Therefore, we attempted to do a clinical study on relation of HbA1c and other risk factors with nephropathy.

II. Material and Methods

This prospective observational study was carried out by involving 120 patients after taking the approval of the protocol review committee and institutional ethics committee.

Type 1 diabetic patients are followed up regularly at least every 3 months. At each visit, HbA1C is measured; body weight and the average dose of total insulin required per day are measured. Height is documented once a year. Blood pressure is systematically measured at diagnosis, and recorded at least once a year. Eye examination, for the presence of diabetic retinopathy, is done by an ophthalmologist at the first visit to the center then followed up a yearly basis. Microalbuminuria is tested in each patient 5 years after the diagnosis of type 1 diabetes, as recommended by ADA[20], and then yearly.

Patients with type 1 diabetes, as defined by ADA[21], admitted to the chronic care center were studied. Only patients admitted to the chronic care center within 12 months of diagnosis of type 1 diabetes mellitus were included, since structural renal abnormalities due to diabetes usually occurs afterward.[22]

Patients were excluded from the study if the duration of diabetes was less than 5 years, since diabetic nephropathy is known to occur after at least 5 years of the disease.[20] Patients were also excluded from the study if they suffered from wolfram syndrome, or had thalassemia or other hemoglobinopathy. Two hundred and ten patients met the inclusion criteria, and 90 patients were excluded. The final sample size was 120 patients.

The following information was obtained: age, gender, date of birth, date of onset of diabetes, date of admission to the center, family history for diabetes, results of microalbuminuria after 5 years of diagnosis, the dates and the results of HbA1C at each visit, BMI at baseline and blood pressure. Patients (micro-albuminureavs non-microalbuminurea) were selected based on a cutoff point of 24 h urine microalbumin of >30 mg/24 h on more than two occasions.

Acceptable metabolic control was defined as having a mean HbA1C <8% and a poor metabolic control denoted a mean HbA1C P8%. Although the definition of poor vs acceptable metabolic control is not standardized, our definition was based on our assay methodology. Results were considered significant at the 5% critical level ($p < 0.05$).

III. Results

The sample analyzed consisted of 120 type 1 diabetic patients, 67 females and 53 males, aged 10–30 years were included in this study. 20 among 120 (16.67%) developed nephropathy after 5 years of onset of diabetes.

As shown in Table 1, there was no association between gender and the development of diabetic nephropathy ($p = 0.95$). There were no significant group differences in the ‘‘age at onset of diabetes” or ‘‘time period from the onset of diabetes till admission to the chronic care center” ($p = 0.48$ and $p = 0.81$, respectively). BMI at first visit for those who developed nephropathy was not significantly different from the BMI at first visit for those who did not have evid ence of nephropathy ($p = 0.41$). There was no significant difference in the outcome between those with and without family history of diabetes. Hypertension was omitted, because of no variability, as patients were not hypertensive.

Table 1: Main characteristics of the study population in relation to the development of diabetic nephropathy

Parameter	Nephropathy N = 20	No nephropathy N = 100	p- value
Gender [n (%)]a			
Male	9 (45)	44 (44)	0.95
Female	11 (55)	56 (56)	
Age at onset (years)	11.95 ± 5.6	11.13 ± 4.10	0.48

Time period from onset of diabetes to admission to CCC (years)	3.97 ± 4.3	3.73 ± 4.3	0.81
BMI at baseline (kg/m2)	19.85 ± 5.3	19.05 ± 3.5	0.41
Family history of diabetes [n (%)]b			
Positive	10 (50)	58 (58)	
Negative	10 (50)	42 (42)	0.36
Mean HbA1C (%)	9.5 ± 1.7	8.6 ± 1.2	0.004
Fluctuations in HbA1C [n (%)]			
Present	12 (60)	54 (54)	
Absent	8 (40)	46 (46)	0.05

Data are means ± SD unless otherwise specified. a [n (%)] indicates the number in each category and (percentage). b Totals do not add up to 120 due to missing data.

The mean HbA1C per individual was 8.65 ± 1.3 in the whole sample. As shown in Table 1, mean HbA1C was 9.5 ± 1.7% among those who developed nephropathy compared to a mean of 8.6 ± 1.2% for those who did not develop nephropathy, and was statistically significant between the two groups (p = 0.004).

The association between fluctuations in HbA1C and diabetic nephropathy is shown in Table1. Among those who developed nephropathy, 10 of 20(60%) had fluctuations in HbA1C; compared to those who do not develop nephropathy 54 of 100 (54%) had fluctuations in HbA1C (p = 0.05).

In order to identify the predictors for diabetic nephropathy, we performed a multivariate analysis, by entering all risk covariates into a multiple logistic regression analysis (Table 2). Results from the full model (referred to as Model 1) revealed that mean HbA1C was the only significant predictive factor; all other variables were not significant. Since our hypothesis is to test whether the presence of fluctuations in HbA1C predicts the development of nephropathy adjusting for the mean HbA1C, we further studied three other models one including the two covariates the mean and the ''fluctuations" in HbA1C (referred to Model 2), another model including only mean HbA1C as a covariate (referred to as Model 3) and the last model including the fluctuations in HbA1C (Model 4). The Model 2 leads to a smaller BIC than Model 3 (BIC dropped from 101.4 to 104.7), indicating positive evidence for a better fit. We also noticed that the odds ratio of the mean HbA1C decreases from 1.76 to 1.56 when the covariate ''fluctuations" is added to the model and becomes closer to 1. Considering Model 4, the odds ratio of the fluctuations in HbA1C is 4.18; however when adjusting for the mean HbA1C (Model 2), the odds ratio dropped to 2.35 and the fluctuations in HbA1c was no more a significant predictor factor.

Table 2: Multivariate analysis for the prediction of diabetic nephropathy

Parameter	Odds ratio Model 1	(95%CI)	Model 2	Model 3	Model 4
Average mean of HbA1C	1.67 (1.04;	2.69)	1.56 (1.02; 2.39)*	1.76 (1.19; 2.60)*	
Fluctuations in HbA1C	1.90(0.43;	8.42)	2.35 (0.57; 9.78)		4.18 (1.14; 15.32)*
Gender	0.86(0.28;	2.64)			
Family history	1.33 (0.43;	4.14)			
Age at onset	1.07(0.89;	1.27)			
Time between onset of diabetes till admission to CCC	0.94 (0.81;	1.09)			
Baseline BMI	0.94 (0.76;	1.15)			
BIC	—123.41		—104.72	—101.41	—104.23

IV. Discussion

WHO multicentric study of vascular disease in diabetes, observed a wide geographic variation in prevalence of nephropathy i.e. 2.4% from Hong Kong, 23% from Delhi to 37% from Oklahoma, USA21. These geographical and population variation in prevalence of diabetic nephropathy could be due to real ethnic variation in the susceptibility to diabetic nephropathy i.e. genetics, poor glycaemic control, hypertension or other socioeconomic, cultural and environmental factors. Several studies indicated that HbA1c may show a glycaemic threshold with micro and macro-vascular complications of diabetes, suggesting it may

additionally be useful biomarker to identify individuals at risk for different vascular complications.[23,24,25] However, in our study, the duration of diabetes was set to 5 years after diagnosis. Our finding that the age at onset of diabetes is not associated with the development of diabetic nephropathy is com- mensurate with recent data[26]; however, as in their study, we did not account for pubertal staging.[27]

The results of our study, like many other reports, did not show an association between gender and the development of diabetic nephropathy. This contrasts with a previousfinding by Holl et al., showing an impact of female gender on the development of insidiousnephropathy.[28] Any association between gender and nephropathy should take into consideration the pubertal stage since the hormonal effects could be at the base of this difference. Data on the association between BMI, an index of metabolic state, and the development of diabetic nephropathy, is scarce.[28] In our study, BMI was measured at the first visit to the center, when most of the patients had poor metabolic control that might have negatively affected the weight. Although the baseline BMI was found to be associated with the development of microvascular complications[29], the impact of BMI was apparent only at higher values. Follow- ing BMI longitudinally and accounting for pubertal changes would help in establishing the associations between BMI and diabetic nephropathy.

Metabolic control was the only established and consistent predictor for the development of diabetic nephropathy. In reviewing the literature, different measures have been used in order to study the association between metabolic control and diabetic nephropathy. The mean HbA1C is repeatedly used[30,27]; the median has also been used as a summary measure.[31] Based on the results of our study, the mean HbA1C remains the only significant predictor for the development of diabetic nephropathy in type 1 diabetic patients, even after adjusting for ''fluctuations''. The use of ''fluctuations'' in HbA1C as a longitudinal measure for the change in the metabolic state is original. It may better reflect the changes in ambient glycemia within one individual. This latter was found to be the culprit in the development of diabetic nephropathy through activation of the proteinase C[32], upregulating the heparanase expression[33], enhancing sensitivity to TGF beta 1[34] and increasing VEGF (vascular endothelial growth factor) expression.[35] Our data showed that ''fluctuations'' in HbA1C predicted the incidence of nephropathy, based on the positive evidence that the model including fluctuations fits the data better. This may have many implications: first, these findings may help to achieve a better understanding of the pathophysiology of diabetic nephropathy, since they suggest that, although this latter is accelerated by the chronic hyperglycemia (manifested as mean HbA1C), it is much worse during acute increases in glycemia which is reflected by fluctuations in HbA1C. Second, our data highlight the issue that a single jump in HbA1C have a durable effect, this agrees with the hypothesis of ''long time- glycemic memory'' and supported by findings from DCCT on microvascular complications. Third, as diabetic nephropathy has an insidious onset, one large increment in HbA1C during the first 5 years, would be an indicator of a development of nephropathy well before the appearance of microalbuminuria.

Nevertheless, our data were unable to establish the association between fluctuations in HbA1C and the development of nephropathy in diabetics with acceptable control. The sample size was small to permit the comparison between the different groups; this was well seen by the wide confidence intervals. Interestingly, taking the whole model, the mean HbA1C explains 10% the prediction for the development of diabetic nephropathy. Other factors, such as genetic predisposition, have been known to be associated with the development of nephropathy. Family history of hypertension[36], kidney disease and other cardio-vascular risk factors[37], were used as a measure for genetic predisposition.

V. Conclusion

We concluded that the type 1 diabetic patients who have a similar mean HbA1C, in the long run, may behave differently in terms of developing nephropathy, depending on the fluctuations in HbA1C and more precisely, depending on the frequency of the acute jumps in the HbA1C.

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Global Journal of Medical Research: F
Diseases
Volume 22 Issue 4 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

O papel da atenção primária à saúde na prevenção e no estadiamento da AIDS / HIV

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Abstract- The Aids is a pathology with high incidence in the teenagers, once the manifestation occurs between seven to ten years after the infection, said that this is the incubation period. Despite the emergence in the late 80 years in the United Estates, there is no cure, having only treatment and prophylaxis, so the APS and SUS playing the important role in this issue. Since it is a pathology that affects the immune system, its evolution has several variants, since each person's organism functioned differently at the same stimuli. The clinical consequences of HIV infection range from acute syndrome associated with primary infection to a prolonged asymptomatic phase culminating in advanced disease. (KASPER et al, 2013) Treatment is carried out based on antiretroviral medicinal products (ARS), with the intention of prolonging survival and improving quality of life by reducing viral load and reconstitution of the individual's immune system.

Keywords: *aids, HIV, infection, treatment.*

GJMR-F Classification: *DDC Code: 616.9 LCC Code: RC111*

Strictly as per the compliance and regulations of:

O papel da atenção primária à saúde na prevenção e no estadiamento da AIDS / HIV

Ana Beatriz Marques Ferreira Da Silva [α], Isabella Oliveira Rios [σ], Laura Botelho Ramos Godinho [ρ], Polyana Grain Paes Rodrigues [ω], Fábio Luiz Fully Teixeira [¥] & Lucas Capita Quarto [§]

Resumo- A Aids é uma patologia com alta incidência em adolescentes, visto que a manifestação ocorre entre sete a dez anos após a infecção, dito esse o seu período de incubação. Apesar do surgimento da doença ter se dado em meado dos anos 80 tendo início nos Estados Unidos, não existe cura para a mesma, tendo apenas medidas de tratameto e profilaxia, tendo assim as APS e o SUS execendo o papel importante nesse quesito. Visto que é uma patologia que acomete o sistema imunológico a sua evolução possui diversas variantes, uma vez que o organismo de cada pessoa funcionada de forma diferente ao mesmo estímulo. As consequências clínicas da infecção pelo HIV abrangem um espectro que varia da síndrome aguda associada à infecção primária até uma fase assintomática prolongada que culmina na doença avançada. (KASPER et al, 2013) O tratamento é realizado baseando-se em medicamentos antirretrovirais (ARS), com a pretensão de prolongar a sobrevida e melhorar a qualidade de vida, pela redução da carga viral e a reconstituição do sistema imunológico do indivíduo. Foi realizada pesquisa em plataforma online como o Google Acadêmico, Scielo, BVS, com a intensão de expor os aspectos necessários a compreensão da população sobre o diagnóstico, manifestação da doença, tratamento, profilaxias e atenção básica.

Palavras-chave: *aids, HIV, infeção, tratamento.*

Abstract- The Aids is a pathology with high incidence in the teenagers, once the manifestation occurs between seven to ten years after the infection, said that this is the incubation period. Despite the emergence in the late 80 years in the United Estates, there is no cure, having only treatment and prophylaxis, so the APS and SUS playing the important role in this issue. Since it is a pathology that affects the immune system, its evolution has several variants, since each person's organism functioned differently at the same stimuli. The clinical consequences of HIV infection range from acute syndrome associated with primary infection to a prolonged asymptomatic phase culminating in advanced disease. (KASPER et al, 2013) Treatment is carried out based on antiretroviral medicinal products (ARS), with the intention of prolonging survival and improving quality of life by reducing viral load and reconstitution of the individual's immune system. Research was carried out on an online platform such as Google Scholar, Scielo, BVS, with the intention of exposing the necessary aspects for the population to understand about the diagnostic, manifestation of the disease, treatment, prophylaxis and the primary care.

Keywords: *aids, HIV, infection, treatment.*

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I. Introdução

A AIDS surgiu em meado dos anos 1980, sendo os primeiros casos documentados em 1981 em San Francisco nos EUA, aonde foi dado como reconhecimento da síndrome e no Brasil ocorreu em 1982, no estado de São Paulo. (AGNES CAROLINE S. et al, 2007).

Tendo conhecimento de que o período de aparecimento da síndrome a área científica e médica estava começando a se desenvolver de maneira significativa, tendo em vista que o Brasil tinha acabado de passar pelo governo Geisel aonde (1974-1979), aonde tiveram iniciativas de diversas políticas sociais, incluindo o Sistema Nacional de Saúde (SNS) em 1975. Os pacientes que são acometidos pelo HIV não possuem uma boa imagem diante da sociedade, principalmente pelo fato de que sua aparição teve grande parte dos casos sendo em homossexuais, assim como hemofílicos e usuários de drogas, causando um abalamento na percepção da população quanto a doença. (KEVIN M. et al, 2012; AGNES CAROLINE S. et al, 2007; ARISTIDES B. et al, 2009)

Em contraposição ao impacto causado pela doença no cotidiano do paciente, o pós- acometimento dos mesmos se dá através de tratamento com medicamentos antirretrovirais (ARV), assim como prevenção de disseminação provocada por métodos contraceptivos e campanhas geradas pelo SUS. (ALEXANDRE R. et al, 2010)

Nos últimos anos foi possível estipular uma alta incidência do vírus HIV no Brasil, sendo em 2008 mostrado que cerca de 600 mil pessoas portam o vírus, com isso pode se observar o quanto a população é acometida tornando assim de extrema importância a participação da saúde pública. Independente do avanço do vírus da imunideficiência humana (HIV), a atenção básica possui grande papel visto que existe acompanhamento aos pacientes, prevenção, indicação de exames e medicamentos, além das campanhas. (Ministério da Saúde, 2008)

Como é de conhecimento comum uma das formas de infecção pelo vírus do HIV se faz pelo ato sexual desprotegido, acaba por ter como característica a maior incidência em adolescentes, visto que a patologia se manifesta entre sete a dez anos após a

infecção, dito esse o seu período de incubação. (MELINA MAFRA T. et al, 2011)

O objetivo deste trabalho é realizar uma revisão visando expor aspectos necessários a compreensão da população sobre a manifestação da doença, diagnóstico, tratamento, tipos de profilaxia e a importância da atenção básica. Deste modo pretendendo reduzir a quantidade de pessoas com a doença, assim como a promoção da prevenção da Aids e o HIV, além de uma maior conscientização da população sobre a enfermidade.

II. Manifestações da Doença

Segundo Veronesi (2015), as mulheres adultas e jovens estão cada vez mais sendo afetadas pela aids, representando 50% das pessoas que vivem com o vírus. Estima-se que haja, atualmente, 660 mil pessoas infectadas com o HIV no Brasil.

O HIV é um vírus de RNA de fita simples, que, uma vez em seu hospedeiro, transcreve este material em DNA (transcrição reversa) que se integra ao núcleo celular de suas células-alvo. A replicação viral é a principal característica do retrovírus. O HIV infecta linfócitos e macrófagos que têm em sua superfície o marcador CD4, mas pode infectar outras células, como as dendríticas. A infecção seletiva de linfócitos CD4+, importantes organizadores da resposta imune adaptativa, é o marco fisiopatológico da doença. (VERONESI, 2015)

De acordo com Veronesi (2015), a depleção dos linfócitos TCD4+ leva à uma desorganização da resposta imune e aumenta a suscetibilidade de processos infecciosos, principalmente por germes intracelulares como as microbactérias, fungos e parasitas, bem como de processos neoplásicos como o linfoma de células B e o sarcoma de Kaposi.

Tão importante quanto a síndrome da imunodeficiência adquirida (aids), decorrente de depleção linfocitária e, geralmente, reativação de infecções latentes (infecções oportunistas), é a doença causada diretamente pelo HIV, pela ativação inflamatória e processos degenerativos, contribuindo com o aumento de doenças cardiovasculares e cerebrovasculares nessa população. (VERONESI, 2015) Segundo Veronesi (2015), a evolução da doença em um indivíduo decorre de como o sistema imune interage com o vírus. Respostas exacerbadas podem se manifestar com doenças oportunistas, ainda na fase aguda, e progressão rápida para aids em poucos anos. Já uma resposta mais modulada pode manter a doença latente por muitos anos.

As consequências clínicas da infecção pelo HIV abrangem um espectro que varia da síndrome aguda associada à infecção primária até uma fase assintomática prolongada que culmina na doença avançada. É mais conveniente considerar a doença causada pelo HIV como um processo com a infecção primária e progride em várias fases. A replicação viral ativa e a disfunção imunológica progressiva ocorrem ao longo de todas as fases da evolução da infecção pelo HIV na maioria dos pacientes. (KASPER et al, 2013).

a) Infecção aguda pelo HIV

Estimativas sugerem que 50 a 70% dos indivíduos infectados pelo HIV apresentam uma síndrome clínica aguda de 3 a 6 semanas depois da infecção primária. Estudos demonstram variáveis graus de gravidade clínica e com isso, sugere-se a soroconversão sintomática que leva o indivíduo a buscar um atendimento médico indica risco mais alto de evolução acelerada da doença, não parece haver qualquer correlação entre o nível da viremia inicial da infecção aguda e a evolução subsequente da doença causada pelo HIV.

Segundo Veronesi (2015), o coito anal receptivo é a forma com maior probabilidade de adquirir infecção, pois no canal anal há grande quantidade de células dendríticas e linfócitos. A mais provável alteração acontece com as células dendríticas, por receptores de manose (C-Lectina) que interagem com gp120 (glicoproteína de superfície do HIV), iniciando o processo de entrada viral.

A via receptora vaginal é a segunda forma mais frequente de transmissão. A transmissão para o parceiro ativo também é possível, porém depende de vários fatores, como intensidade do ato sexual, microlesões penianas, presença de lesão na mucosa vaginal ou anal, decorrente de trauma da relação ou doença sexualmente transmissível (sífilis, por exemplo). Outras formas de transmissão, como sexo oral, aleitamento materno, uso de drogas injetáveis e hemoderivados contaminados, figuram como formas menos frequentes de transmissão, porém não menos importantes. (VERONESI, 2015)

Após duas horas do contato do vírus com uma das mucosas relacionadas (anal, vaginal ou peniana), o HIV atravessa a barreira mucoepitelial protetora e pode entrar em contato com macrófagos teciduais, linfócitos e células dendríticas, estas com a capacidade de apresentar antígenos, carreando o vírus até o grupamento linfoide mais próximo. Esse processo ocorre em até 24 horas após o contato e, como não houve integração do genoma viral com o DNA de uma célula hospedeira, ainda há chance de evitar a infecção. (VERONESI, 2015)

De acordo com Veronesi (2015), o vírus é apresentado ao linfócito TCD4+ virgem e entregue ao seu alvo sem ter sido reconhecido pelo sistema imune. Começa então a replicação viral no linfonodo, atingindo toda subpopulação de linfócitos CD4+ presente. Essa é a "fase eclipse", com duração de 7 a 21 dias, período no qual o RNA viral geralmente não pode ser detectado no plasma do paciente. Com o tráfego celular (cell

traffic king), esses linfócitos carrearão o vírus pelas próximas 2 a 3 semanas a todas as partes do organismo, principalmente os linfócitos do tecido associado a mucosa (MALT) intestinal.

No momento de grande viremia, de acordo com Veronesi (2015), surgem os sintomas da infecção aguda: manifestações inespecíficas, como febre, linfadenomegalia generalizada, anorexia, mal-estar ou até mesmo esplenomegalia, hepatomegalia, icterícia, rash citâneo, plaquetopenia e diarreia, esta que configura como um dos sintomas mais frequentes e muitas vezes leva o paciente à investigação de doença inflamatória intestinal, pois pode vir acompanhada de muco.

O diagnóstico de infecção aguda por HIV-1 requer um alto índice de suspeita clínica por médicos de todas as especialidades, uma vez que o quadro clínico varia desde febre ao esclarecimento de manifestações gastrointestinais exuberantes, e o uso correto de testes diagnósticos laboratoriais específicos. O diagnóstico de infecção por HIV deve ser inicialmente avaliado por meio de um teste ELISA (enzime linked immuno sorbent assay) ou ensaio imunoenzimático. Se o teste ELISA for positivo, um teste Western-blot é feito para confirmar que o resultado do teste ELISA é específico para o HIV. Se os testes ELISA e Western-blot forem negativos ou indeterminados e houver suspeita de síndrome retroviral aguda, uma carga viral de HIV-1 deve ser obtida, porém este teste não deve ser utilizado de rotina para diagnóstico, uma vez que podem ocorrer falso-negativos, a depender da quantidade de vírus circulante. Com o limite de detecção cada vez menor pela evolução do teste, futuramente, essa particularidade desaparecerá. O vírus pode ser detectado por reação em cadeia da polimerase (PCR), durante os sete primeiros dias após a infecção, tornando esse teste uma ferramenta útil se uma intervenção terapêutica precoce for necessária. (VERONESI, 2015)

Segundo Kasper, a síndrome é típica de uma infecção viral aguda e foi comparada a mononucleose infecciosa aguda. Em geral, os sinais e sintomas persistem por uma a várias semanas e regridem gradativamente à medida que a resposta imune ao HIV se desenvolve e os níveis de viremia plasmática diminuem. Alguns autores relataram infecções oportunistas durante essa fase da infecção, refletindo a imunodeficiência resultante das contagens reduzidas de célula TCD4+ e, provavelmente, também a disfunção dessas células em consequência das anormalidades celulares induzidas pelas proteínas virais e pelas citocinas endógenas.

b) Estágio assintomático – latência clínica

Embora o intervalo entre a infecção inicial e o início da doença clínica seja amplamente variável, o intervalo médio para os pacientes não tratados é de cerca de 10 anos. Conforme ressaltado antes, a doença causada pelo HIV com replicação viral ativa é contínua e progressiva durante esse período assintomático. A taxa de progressão da doença correlaciona- se diretamente com os níveis de RNA de HIV. Os pacientes com níveis plasmáticos altos de RNA do HIV evoluem para a doença sintomática mais rapidamente que os indivíduos com baixos níveis de RNA do HIV.

Alguns indivíduos, designados como pacientes sem progressão da doença em longo prazo, apresentam pouco ou nenhum declínio das contagens de células TCD4+ por intervalos longos. Em geral, esses indivíduos têm níveis extremamente baixos de RNA viral,

Sinais e sintomas

A infecção aguda pelo HIV-1 apresenta seus sinais e sintomas dentro de alguns dias a semanas após a exposição inicial. Os sinais e sintomas mais comuns incluem febre, fadiga, erupção cutânea que geralmente é maculopapular, mas pode ter apresentações multifacetadas como dor de cabeça, linfadenopatia, faringite, mialgia, artralgia, meningite asséptica, retro – dor orbitária, perda de peso, depressão, desconforto gastrointestinal, suores noturnos e úlceras orais ou genitais. A doença aguda pode durar de alguns dias a mais de 10 semanas, mas a duração geralmente é inferior a 14 dias. (SCHACKER T et al, 1996)

Uma avaliação para infecção aguda por HIV-1 deve ser realizada se um paciente apresentar sinais e sintomas que sejam consistentes com o diagnóstico e uma história de exposição a uma pessoa com infecção conhecida ou possível pelo HIV-1. A infecção aguda também deve ser considerada em pessoas que apresentam uma doença sexualmente transmissível.

1. *Diagnóstico*

A doença pode ou não ter expressão clínica logo após a infecção, sendo importante que o profissional saiba conduzir a investigação laboratorial após a suspeita de risco de infecção pelo HIV. É importante o entendimento da dinâmica da variação viral ou seus marcadores e o curso temporal em indivíduos depois da exposição ao HIV. Além disso, é imprescindível reconhecer a diferença entre a janela imunológica e a soroconversão. (Ministério da Saúde, 2010)

O diagnóstico de infecção aguda por HIV-1 não pode ser feito com testes sorológicos padrão. Os ensaios de imunoabsorção enzimática recombinante (ELISAs) comumente usados para diagnosticar a infecção pelo HIV-1 estabelecida são geralmente negativos em pessoas que apresentam infecção aguda. Os testes sorológicos primeiro tornam-se positivos aproximadamente 22 a 27 dias após a infecção aguda.

Os testes rápidos (TR) são imunoensaios (IE) simples, com resultados em até 30 minutos, realizados

preferencialmente de forma presencial em ambiente não laboratorial com amostra de sangue total obtida por punção digital ou amostra de fluido oral.

Tendo em vista que os TR são desenvolvidos para detectar anticorpos anti-HIV em até 30 minutos, em comparação com os testes de imunoensaios utilizados em laboratórios, os dispositivos são otimizados para acelerar a interação antígeno/anticorpo. Isso requer a utilização de uma maior concentração de antígeno e da detecção de complexo antígeno/ anticorpo com reagentes sensíveis à cor, como o ouro coloidal.

Os TR são ideias para fornecer resultados no mesmo dia em uma variedade de situações como: populações – chave, populações prioritárias, parcerias de pessoas vivendo com HIV/aids, acidentes biológicos ocupacionais, gestantes que não tenham sido testadas durante o pré-natal ou cuja idade gestacional não assegure o recebimento do resultado do teste antes do parto, parturientes e puérperas que não tenham sido testadas no pré-natal ou quando não se conhece o resultado do teste no momento do parto, abortamento espontâneo, independentemente da idade gestacional, pessoas com diagnóstico de tuberculose e pacientes com diagnóstico de hepatites virais. (Ministério da Saúde, 2002)

2. Tratamento

A abordagem clínica – terapêutica do HIV tem-se tornado cada vez mais complexa, em virtude da velocidade do conhecimento acerca desse agente. (Ministério da Saúde, 2010)

Segundo o Ministério de saúde, os objetivos do tratamento são: prolongar a sobrevida e melhorar a qualidade de vida, pela redução da carga viral e a reconstituição do sistema imunológico do indivíduo.

O atendimento é garantido pelo SUS, por meio de uma ampla rede de serviços. O Brasil é um dos poucos países que disponibiliza, integralmente, a assistência ao paciente com Aids. (Ministério da Saúde, 2010)

3. Profilaxias

A prevenção de infecções oportunistas em indivíduos infectados pelo HIV é de grande efetividade e proporciona uma redução significativa de morbidade. Essa prevenção possui três grandes aspectos:

Prevenção de exposição

É uma estratégia que reduz o risco do aparecimento de infecções oportunistas, consistindo no desenvolvimento de atitudes e estilo de vida capazes de diminuir o contato com patógenos oportunistas e agentes de co-infecções.

Profilaxia primária

Tem como objetivo o desenvolvimento de doenças em pessoas com exposição prévia estabelecida ou provável.

Profilaxia secundária

Possui como objetivo evitar a recidiva de infecções oportunistas que já tenham ocorrido.

III. Atenção Primária à Saúde

A Atenção Primária à Saúde (APS) apresenta-se como uma estratégia de organização da atenção à saúde voltada para responder de maneira regionalizada, contínua e sistematizada à maior parte das necessidades de saúde de uma população, integrando ações preventivas e curativas, bem como a atenção a indivíduos e comunidades. (MATTA, 2009)

No Brasil, a APS agrega os princípios da Reforma Sanitária, deste modo o Sistema Único de Saúde (SUS) empregou a designação Atenção Básica à Saúde (ABS) para que o modelo assistencial seja reorientado a partir de um sistema integrado e universal de atenção à saúde.

O principal objetivo da ABS é o atendimento inicial ao paciente. Desse modo, seu intuito é dispor sobre a prevenção de doenças, solucionar os possíveis casos de agravos e direcionar os mais graves para níveis de atendimento superiores em complexidade. A ABS funciona, portanto, organizando o fluxo dos serviços nas redes de saúde, dos mais simples aos mais complexos.

É importante sinalizar, ainda, que algumas práticas e ações já são incorporadas à ABS de maneira ampla, como aquelas voltadas à saúde da criança, ao cuidado pré-natal e ao cuidado de pessoas com diabetes e hipertensão. Por outro lado, ações no campo da saúde mental, da reabilitação e de condições como HIV/Aids, ainda que existam, são menos características da atenção básica, ou realizadas nesse espaço de modo mais parcial. (MELO, 2018) Sendo um serviço preeminente da APS.

A evolução da epidemia da Aids permanece desconstruindo hábitos, revendo conceitos e revolucionando costumes em todo o mundo. Como doença sexualmente transmissível alimenta as estatísticas mundiais e se configura como um dos agravos mais comuns à saúde na contemporaneidade. (NAVARRO, 2011)

A complexidade que envolve a HIV/Aids diz respeito não só aos aspectos físicos da doença, mas, principalmente, a discriminação no meio social dos que convivem com o vírus. Ou seja, o que permeia o HIV/Aids não é apenas o medo da contaminação ou as consequências à corporalidade dos acometidos pela doença, mas os julgamentos morais atrelados a ela. Sendo assim, é considerado que todas as pessoas são vulneráveis à infecção pelo HIV e o nível da proporção em maior ou menor, encontra-se relacionada ao contexto social, aos valores pessoais, níveis de exclusão socioculturais e econômicos. Diante da soropositividade, a vulnerabilidade ao adoecimento

está associada à qualidade de vida, aos serviços públicos oferecidos e à sociedade civil organizada.

Neste sentido, desde o início da epidemia, ainda permanece um esforço social e político em divulgar informações que esclareçam a população sobre a doença e ajudem a superar os seus desafios impostos, além de favorecer comportamentos preventivos para diminuir o contágio do vírus.

Estima-se que, no Brasil, cerca de 600 mil pessoas portam o vírus da imunodeficiência humana (HIV). Os últimos boletins evidenciaram mudanças no perfil epidemiológico que, associados aos pactos de saúde, passaram a subsidiar estratégias de atenção e prevenção para as populações vulneráveis identificadas, como as pessoas na faixa da maturidade e terceira idade (Ministério da Saúde, 2008)

No que tange esta perspectiva, faz-se necessário o investimento de políticas públicas de saúde em medidas de prevenção e controle de transmissão, estabelecendo novas possibilidades nas redes de serviços e estratégias de cuidado. No mais, os avanços científicos no tratamento de pessoas soropositivas para a Aids também colaboram para essa abertura.

Recentemente, novas diretrizes nacionais e experiências locais têm colocado a Atenção Básica à saúde em posição de protagonismo no tema do HIV/Aids, com papel de manter e ampliar ações de promoção, prevenção e diagnóstico e de incorporar o acompanhamento de usuários com HIV. Até então, as políticas de HIV/Aids, nas quais o Brasil tem se destacado no cenário mundial, tinham seu componente assistencial desenvolvido principalmente nos serviços especializados. (MELO, 2018)

IV. Promoção da Saúde

Entre os anos de 2011 e 2012, o Ministério da Saúde introduziu novas tecnologias diagnósticas na APS, com destaque, conforme já mencionado, para os testes rápidos (gravidez, sífilis e HIV, entre outros), aumentando o acesso à testagem e ampliando o diagnóstico de HIV na APS em todas as regiões do país.

A partir de 2013, o Ministério da Saúde passou a adotar também diretrizes e recomendações de incentivo ao acompanhamento de pessoas com HIV/Aids (com quadro de baixo risco) na atenção básica dos municípios.

O diagnóstico do HIV é feito por meio de testes laboratoriais ou testes rápidos (TR). O teste laboratorial Elisa é o mais utilizado para diagnosticar a infecção, no qual se procura por anticorpos contra o HIV no sangue. Uma vez que a amostra não apresentar nenhum anticorpo, o resultado negativo é fornecido para a pessoa. Caso seja detectado algum anticorpo anti-HIV, é necessária a realização de outro teste adicional, o teste confirmatório. São usados como testes confirmatórios o Western Blot, o Teste de Imunofluorescência Indireta para o HIV-1, o Imunoblot ou o próprio teste rápido.

O teste rápido para HIV é realizado com uma gota de sangue da ponta do dedo ou por meio do fluido oral (material coletado da mucosa oral - Swab) obtendo o resultado em até 30 minutos. Para o diagnóstico do HIV com o teste rápido, é necessário fazer um teste de triagem (primeiro teste de HIV) e, se este for reagente, outro teste deve ser realizado para confirmar o diagnóstico (teste confirmatório). A infecção por HIV não tem cura, mas possui tratamento, isto é, quanto mais cedo o indivíduo for diagnosticado e tratado, seu sistema imunológico estará reestabelecido melhorando assim a qualidade de vida do mesmo.

Para evitar a infecção pelo HIV, algumas medidas são importantes, como: Usar preservativo em todas as relações sexuais (vaginal, anal e oral); não compartilhar seringas, agulhas e outros objetos perfurocortantes não esterilizados com outras pessoas; Mulheres vivendo com HIV/aids não devem amamentar, e necessitam realizar acompanhamento pré-natal para que sejam tomadas as medidas necessárias à prevenção da transmissão vertical do HIV (da mãe para a criança). O preservativo (masculino e feminino) é o método de barreira mais eficaz para a prevenção do HIV. Além disso, protege contra outras Infecções Sexualmente Transmissíveis (IST) e evita a gravidez não planejada.

Portanto, é papel da Atenção Básica a notificação adequada e competência no cuidado à pessoa vivendo com HIV/Aids (PVHA) as seguintes atitudes:

- Realizar ações de promoção e prevenção direcionadas a fatores de vulnerabilidade, comportamento e estilo de vida.
- Ampliar oferta do diagnóstico, associado aos demais atendimentos prestados, preferencialmente por TR para HIV, hepatites e sífilis na população em geral, populações- chave e prioritárias, mediante demanda espontânea, evitando realização de agendamento.
- Realizar TR em gestante e parceiro(s) sexual(is).
- Realizar acolhimento e aconselhamento.
- Orientar a população sobre novas tecnologias de prevenção (PEP e PrEP, entre outras) e demais informações sobre IST/ HIV/Aids e HV.
- Avaliar e encaminhar, quando necessário, os casos de PEP.
- Ofertar insumos de prevenção (preservativo masculino, feminino) para a população.
- Atualizar o calendário vacinal em todas as idades, conforme orientações do Programa Nacional de Imunizações.

– Notificar no SINAN os casos de HIV, sífilis e hepatites B e C.

V. Considerações Finais

Diante da apresentação das informações e dados obtidos a partir do levantamento bibliográfico indicam que se faz necessário um acompanhamento precoce da população as APS no sentido de manter exames em dia e com isso um aumento da prevenção não somente contra a Aids e o HIV, mas também em relação a outras doenças cotidianas. Precisa-se que haja um maior esforço das autoridades para com as campanhas de conscientização e esclarecimento da população de maneira geral quanto ao seu tratamento e aos fatores de risco.

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Global Journal of Medical Research: F
Diseases
Volume 22 Issue 4 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

Computational Analysis of Possibly Pathogenic Non-Synonymous Single Nucleotide Polymorphisms Variants in HGD Gene

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Abstract- Alkaptonuria (AKU) is an autosomal recessive disorder caused by mutations in the homogentisate-1,2-dioxygenase (HGD) gene leading to the deficiency of HGD enzyme activity. The aim of this study was to use some computational bioinformatics tools to predict the most pathogenic non-synonymous mutations in the HGD gene. The data was retrieved from the SNPs database of the National Center for Biotechnology Information (dbSNPs) (Oct. 2021). The primary sequence of the protein was obtained from the UniProt database (Oct. 2021). The pathogenic effect on the protein structure and function was predicted by GeneMANIA, SIFT, Provean, Polyphen-2, I-Mutant, and Project Hope software. The human HGD gene comprises a total of 423SNPs out of that 348 were found to be synonymous, 75 were missense SNPs (nsSNPs). Analysis of the nsSNPs by SIFT predicts 35 as deleterious and 40 as tolerated ones. Using Provean only 30 were deleterious while 5 SNPs were neutral. Taking the deleterious nsSNPSs to Polyphen-2, 25 nsSNPs were damaging (22 were probably damaging and 3 were possibly damaging), while 5 were benign.

Keywords: *Alkaptonuria (AKU); homogentisate-1,2-dioxygenase (HGD) gene; I-Mutant; Non-synonymous Single Nucleotide Polymorphisms (nsSNPs); Project Hope, and SIFT.*

GJMR-F Classification: *DDC Code: 724 LCC Code: NA500*

Strictly as per the compliance and regulations of:

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Abstract- Alkaptonuria (AKU) is an autosomal recessive disorder caused by mutations in the homogentisate-1,2-dioxygenase (HGD) gene leading to the deficiency of HGD enzyme activity. The aim of this study was to use some computational bioinformatics tools to predict the most pathogenic non-synonymous mutations in the HGD gene. The data was retrieved from the SNPs database of the National Center for Biotechnology Information (dbSNPs) (Oct. 2021). The primary sequence of the protein was obtained from the UniProt database (Oct. 2021). The pathogenic effect on the protein structure and function was predicted by GeneMANIA, SIFT, Provean, Polyphen-2, I-Mutant, and Project Hope software. The human HGD gene comprises a total of 423SNPs out of that 348 were found to be synonymous, 75 were missense SNPs (nsSNPs). Analysis of the nsSNPs by SIFT predicts 35 as deleterious and 40 as tolerated ones. Using Provean only 30 were deleterious while 5 SNPs were neutral. Taking the deleterious nsSNPSs to Polyphen-2, 25 nsSNPs were damaging (22 were probably damaging and 3 were possibly damaging), while 5 were benign. Using SNPs&GO 11 nsSNPs were predicted as disease-related while 14 were predicted to be neutral. Project Hope analysis the mutations according to their size, charge, hydrophobicity, and conservancy. In conclusion, 7 of the predicted mutations were not reported before according to the ClinVar database while the remaining 4 were reported from patients through DNA sequencing. More research is needed to confirm these new mutations in patients.

Keywords: Alkaptonuria (AKU); homogentisate-1,2-dioxygenase (HGD) gene; I-Mutant; Non-synonymous Single Nucleotide Polymorphisms (nsSNPs); Project Hope, and SIFT.

I. Introduction

The HGD gene provides instructions for making Homogentisate oxidase enzyme, which is active mainly in the liver and kidneys. This enzyme participates in a stepwise process that breaks down two amino acids, phenylalanine and tyrosine when they are no longer needed or are present in excess. These two amino acids also play a role in making certain hormones, pigments, and brain chemicals called neurotransmitters (Aliu et al., 2018). Homogentisate oxidase is responsible for a specific step in the breakdown of phenylalanine and tyrosine. Previous steps convert the two amino acids into a molecule called homogentisic acid. Homogentisate oxidase adds two oxygen atoms to homogentisic acid, converting it to another molecule called maleylacetoacetate. Other enzymes break down maleylacetoacetate into smaller molecules that are later used for energy or to make other products that can be used by the body (Berniniet al., 2021). Mutations in the HGD gene inactivate Homogentisate oxidase by changing its structure. Without a functional version of this enzyme, phenylalanine and tyrosine are not broken down properly and homogentisic acid builds up in the body. Excess homogentisic acid and related compounds are deposited in connective tissues such as cartilage and skin, which causes them to darken. Over time, a buildup of this substance in the joints leads to arthritis. Homogentisic acid is also excreted in the urine, making the urine turn dark when exposed to air(Wilson et al., 2021).

Single Nucleotides Polymorphisms (SNPs) responsible for the maximum communal type of hereditary change in humans. Regarding throughout a coding areas of mammalian genomes, 500,000 SNPs fell into it (Shameem et al., 2021).The HGD protein protomer is composed of 445 amino acids (NP_000178.2) and is expressed in the prostate, small intestine, colon, kidney, and liver (Fernández et al., 1996), as well as in osteoarticular compartment cells (chondrocytes, synoviocytes, and osteoblasts) (Laschiet al., 2012).The enzymatic defect in AKU is caused by recessive mutations within the HGD gene (HGNC:4892), a single-copy gene that spans 54363bp of genomic sequence (3q13.33) and is split into 14 exons and codes for the HGD protomer (Zatkova and Nemethova, 2015.). The active form of the HGD protein is organized as a hexamer comprising two disc-like trimers. An intricate network of non-covalent interactions is required to maintain the spatial structure of the protomer, of the trimer andfinally of the hexamer, which can be easily disrupted by variants leading to effects on enzyme function (Titus et al., 2000). Compromising enzyme function, the missense variants are predicted to affect

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the activity of the enzyme by three molecular mechanisms: decrease of stability of individual protomers, disruption of protomer–protomer interactions or modification of residues in the active site region (Nemethova et al., 2016).

The effects of SNPs on HGD protein structure and functions still remains elusive; therefore, in this present study, the deleterious effect of SNPs on HGD gene were analyzedby using various computational databases and bioinformatics tools. Instead of biological experiment confirmation, the study tries to provide a useful method for fast and cost effective screening for pathologic SNPs.

II. Material and Methods

a) Data retrieval

Data was retrieved from the SNP database of the National Center for Biotechnology Information (dbSNP) (http://www.ncbi.nlm.nih.gov/snp). The NCBI SNP database (https://www.ncbi.nlm.nih.gov/snp) was used to access the SNPs of the HGD gene (Oct 2021). The primary sequence of the protein (Uniprot accession number: Q93099) encoded by the HGD_HUMAN gene was obtained from the UniProt database (Oct 2021).

b) Gene MANIA software

Interaction of this gene with other genes was investigated using Gene MANIA (http://genemania.org). It is a flexible user-friendly website for generating hypotheses about gene function, analyzing gene lists, and prioritizing genes for functional assays. Given a query gene list, Gene MANIA finds functionally similar genes using a wealth of genomics and proteomics data. In this mode, it weights each functional genomic dataset according to its predictive value for the query. (Franz,et al., 2018).

c) Functional and structural analysis of the SNPs

Only missense SNPs were selected from the NCBI SNPs database as they can modify the sequence of the amino acid encoded by the protein and have the potential to disturb the structural arrangement and function of the proteins. The functional effect of the SNPs on the protein was investigated using SIFT, Provean, Polyphen-2, SNPs& GO, and PHD-SNPs. The stability of the protein as the result of the mutation was studied using I- Mutant and MUPro, and finally the effect of the nsSNPs on the structure was predicted using Project Hope software.

i. *SIFT (Sorting Intolerant from Tolerant)*

This software was developed by Kumar et al., 2009. It predicts whether an amino acid substitution affects protein function based on sequence homology and the physical properties of amino acids. SIFT uses sequence homology among related genes and domains across species to predict the impact of all 20 possible amino acids at a given position, allowing users to determine which nsSNPs would be of most interest to study by sorting variants by this prediction score. It gives scores to each amino acid residue ranging from zero to one. The SIFT prediction is given as a tolerance index (TI) score ranging from 0.0 to 1.0, which is the normalized probability that the amino acid change is tolerated. The threshold intolerance score for SNPs is 0.05 or less (Amberger et al., 2009).

ii. *Provean (Protein Variation Effect Analysis)*

Is a software tool that predicts whether an amino acid substitution has an impact on the biological function of a protein. Provean is useful for filtering sequence variants to identify nonsynonymous variants that are predicted to be functionally important. The performance of Provean is comparable to popular tools such as SIFT or PolyPhen-2 (Choi et al., 2012). A fast computation approach to obtain pairwise sequence alignment scores enabled the generation of precomputed Provean predictions for 20 single AA substitutions at every amino acid position of all protein sequences in humans and mice (Choi, 2012).

iii. *Polyphen-2 (Polymorphism Phenotyping v2)*

It is a multiple sequence alignment server that aligns sequences using structural information. Input for the PolyPhen-2 server is either a protein sequence or accession number together with sequence position with two amino acid variants. (Ramensky et al.,2002).It estimates the position-specific independent count score (PSIC) for every variant and then determines the difference between them, the higher the PSI, the higher the functional impact of the amino acid on the protein function may be. Prediction outcomes could be classified as probably damaging, possibly damaging or benign according to the score ranging from (0–1) (Adzhubei et al., 2013).

SNPs &GO (Single nucleotide polymorphism & Gene Ontology), PHD-SNP, (Predictor of Human Deleterious SNP)

SNPs & GO, an accurate method that, starting from a protein sequence, can predict whether a mutation is disease-related or not by exploiting the protein functional annotation. SNPs & GO collects in unique framework information derived from protein sequence, evolutionary information, and function as encoded in the Gene Ontology terms, and outperforms other available predictive methods (Calabrese et al., 2009).

d) Prediction of Protein stability

Two software were used to predict the effect of a missense mutation on the protein's stability.

i. *I-Mutant 3.0 http://gpcr2.biocomp.unibo.it/cgi/predictors/I-Mutant3.0/I-Mutant3.0.cgi*

This software offers the opportunity to predict automatically protein stability changes upon single-site mutations starting from protein sequence alone or

protein structure when available. Moreover, it can predict deleterious Single Nucleotide Polymorphism starting from the protein sequence alone. (Capriotti et al., 2006).

ii. *MUpro: http://mupro.proteomics.ics.uci.edu/*

It is a machine-learning approach based on support-vector machines to predict the protein stability changes for single site mutations in two contexts taking into account structure-dependent and sequence-dependent information, respectively (Cheng et al., 2006).

e) Prediction of protein modeling

This was achieved by using project Hope softwarehttps://www3.cmbi.umcn.nl/hope/. HOPE is a next-generation software application for automatic mutant analysis. HOPE was designed to explain the molecular origin of a disease-related phenotype caused by mutations in human proteins. HOPE collects information from data sources such as the protein's 3D structure and the UniProt database of well-annotated protein sequences. For each protein, this data is stored in a PostgreSQL-based information system. A decision scheme is used to process these data and predict the effects of the mutation on the 3D structure and the protein's function (Das et al., 2022).

III. Results

Using Gene MANIA, the HGD gene was found to have an association with 20 other different genes. Among these is the HPD gene which provides instructions for making the 4-hydroxyphenylpyruvate dioxygenase enzyme. This gene is the second in a series of five enzymes that work to break down the amino acid tyrosine, a protein-building block found in many foods. Figure (1) and Table (1). The physical interaction and co-expression of this gene with other related genes is shown in Figure (1).

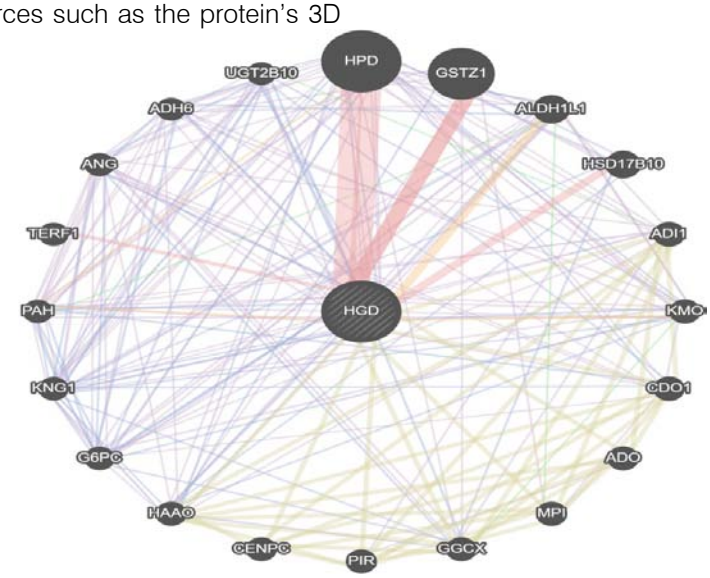


Figure 1: Gene MANIA result for HDG Gene

Table 1: Gene Description Rank Using GeneMANIA

Gene	Description
HGD	homogentisate 1,2-dioxygenase
HPD	4-hydroxyphenylpyruvate dioxygenase
GSTZ1	glutathione S-transferase zeta 1
ALDH1L1	aldehyde dehydrogenase 1 family member L1
HSD17B10	hydroxysteroid 17-beta dehydrogenase 10
ADI1	acireductone dioxygenase 1
KMO	kynurenine 3-monooxygenase
CDO1	cysteine dioxygenase type 1
ADO	2-aminoethanethiol dioxygenase
MPI	mannose phosphate isomerase
GGCX	gamma-glutamyl carboxylase
PIR	Pirin
CENPC	centromere protein C
HAAO	3-hydroxyanthranilate 3,4-dioxygenase
G6PC	glucose-6-phosphatase catalytic subunit

KNG1	kininogen 1
PAH	phenylalanine hydroxylase
TERF1	telomeric repeat binding factor 1
ANG	Angiogenin
ADH6	alcohol dehydrogenase 6
UGT2B10	UDP glucuronosyltransferase family 2 member B10

The SNPs of the HGD gene systematically examined in this study were retrieved from the NCBI SNP database. The protein was retrieved from UniProtKB. The human HGD gene comprises a total of 423 SNPs out of that 348 were found to be synonymous, 75 were missense SNPs (nsSNPs). Analysis of the nsSNPs by SIFT predicts 35 as deleterious and 40 as tolerated ones. Using Provean only 30 were deleterious while 5 SNPs were neutral. Taking the deleterious nsSNPSs to Polyphen-2,25 nsSNPs were damaging (22were probably damaging and 3 were possibly damaging), while 5 were benign. Results were shown in Tables (2) and (3).

Table 2: The Results of Different Software

Software	Results
Retrieved SNPs	348 synonymous and 75 non- synonymous
SIFT	35 Deleterious and 40 Tolerated
Provean	30 deleterious 5 neutral
Polyphen-2	22 probably damaging 3 possibly damaging 5 benign
SNPs & GO and PHD SNPs	11 SNPs had a disease association 14 neutral

Table 3: List of nsSNPs predicted to be deleterious by SIFT, Provean, and PolyPhen-2coding region of HGD gene

SNP ID	Amino Acid Change	SIFT prediction	SIFT Score	PROVEAN Prediction (cutoff= -2.5)	PROVEAN score	POLYPHEN-2 Prediction	POLYPHEN-2 Score
rs138558042	P373L	Deleterious	0.002	Deleterious	-9.802	Probably Damaging	1
rs368717991	G360R	Deleterious	0	Deleterious	-7.572	Probably Damaging	1
rs139501220	M339I	Deleterious	0.002	Deleterious	-3.677	Probably Damaging	0.976
rs143396290	D326N	Deleterious	0.045	Neutral	-2.162		
rs199927284	V316F	Deleterious	0.001	Deleterious	-4.804	Probably Damaging	0.999
rs372084813	L122F	Deleterious	0.001	Deleterious	-5.44	Probably Damaging	1
rs201529624	P114R	Deleterious	0.186	Neutral	-0.592		
rs201529624	P308R	Deleterious	0.016	Deleterious	-7.053	Benign	0.311
rs143556739	R307C	Deleterious	0.047	Deleterious	-3.91	Possibly Damaging	0.618
rs143556739	R113C	Deleterious	0.047	Deleterious	-4.403	Probably Damaging	0.999
rs372420052	T105A	Deleterious	0.023	Neutral	0		
rs372420052	T299A	Deleterious	0.025	Deleterious	-4.913	Probably Damaging	0.996
rs148641817	A293E	Deleterious	0.014	Deleterious	-3.147	Possibly Damaging	0.933
rs148641817	A99E	Deleterious	0.014	Deleterious	-7.351	Possibly Damaging	0.618
rs200382812	L85M	Deleterious	0.048	Deleterious	-7.378	Probably Damaging	0.994
rs199536408	G41D	Deleterious	0	Deleterious	-5.638	Probably Damaging	1

rs199536408	G4D	Deleterious	0	Deleterious	-4.548	Probably Damaging	0.994
rs199536408	G198D	Deleterious	0.001	Deleterious	-6.729	Probably Damaging	1
rs368256121	V24I	Deleterious	0.042	Deleterious	-2.731	Probably Damaging	0.784
rs375283568	E168K	Deleterious	0.001	Deleterious	-3.978	Probably Damaging	1
rs375396766	H117L	Deleterious	0.019	Neutral	-1.931		
rs375283568	E11K	Deleterious	0.004	Deleterious	-6.639	Probably Damaging	1
rs140543217	L163F	Deleterious	0.009	Deleterious	-3.907	Probably Damaging	0.992
rs140543217	Y6F	Deleterious	0.037	Deleterious	-3.52	Probably Damaging	1
rs375396766	P158L	Deleterious	0.018	Deleterious	-9.94	Probably Damaging	0.998
rs375396766	H117L	Deleterious	0.019	Deleterious	-3.974	Benign	0.002
rs374473331	G123E	Deleterious	0	Deleterious	-7.547	Probably Damaging	1
rs374473331	G82E	Deleterious	0.001	Deleterious	-2.778	Benign	0.005
rs143267384	E101V	Deleterious	0.032	Deleterious	-3.128	Benign	0.017
rs143267384	E60V	Deleterious	0.044	Deleterious	-13.647	Probably Damaging	1
rs370003137	S67P	Deleterious	0.011	Deleterious	-4.446	Benign	0.374
rs370003137	S26P	Deleterious	0.036	Neutral	0		
rs200808744	R53Q	Deleterious	0.019	Deleterious	-3.724	Probably Damaging	1
rs373921680	E42A	Deleterious	0.001	Deleterious	-5.639	Probably Damaging	1
rs370453859	G11E	Deleterious	0.004	Deleterious	-6.573	Probably Damaging	1

Using additional software SNPs & GO showed that 11 SNPs had a disease effect and 14 were neutral. For protein stability, I-Mutant software was used, all disease-related mutations resulting from SNPs&Go were predicted to decrease the protein stability with varied probabilities. The results were shown in Table (4).

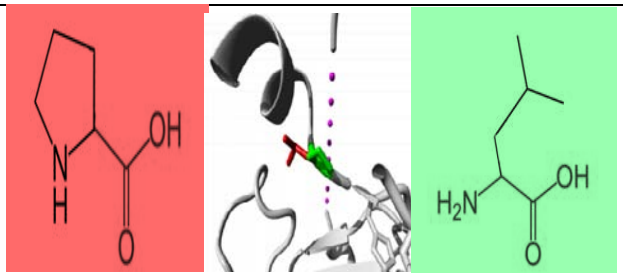
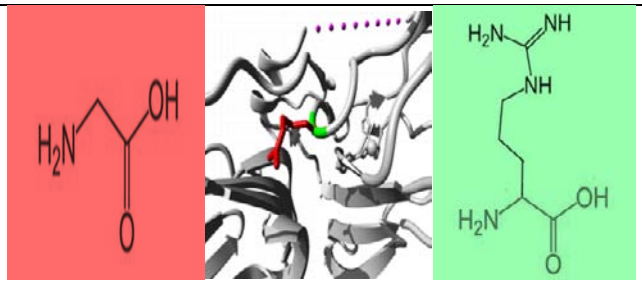
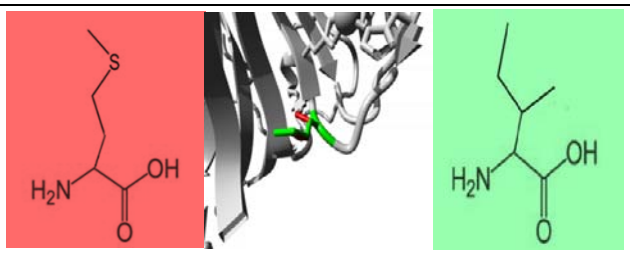
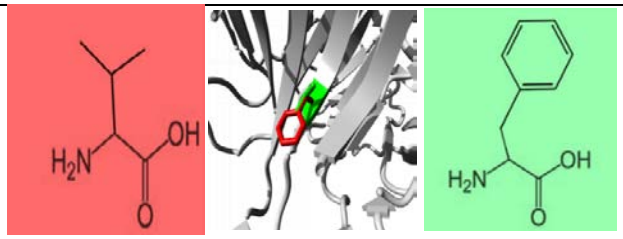
Table (4): Results of SNPs & GO, PHD SNP and I-Mutant software

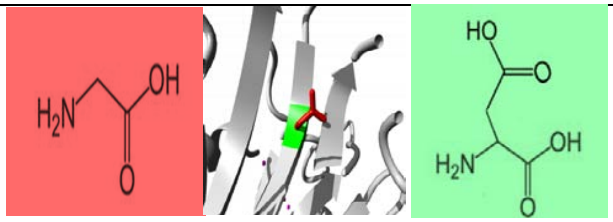
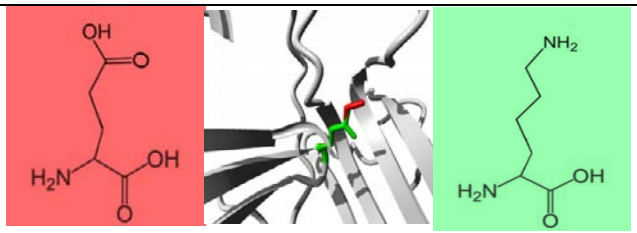
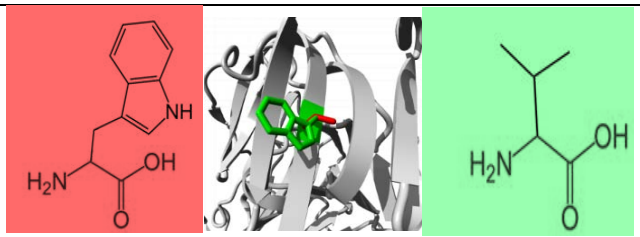
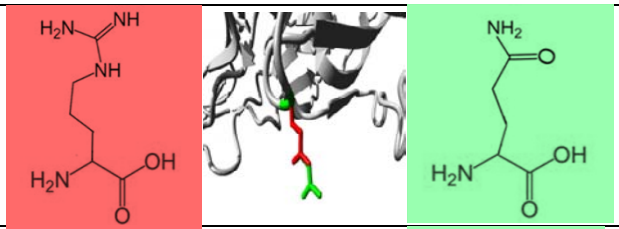
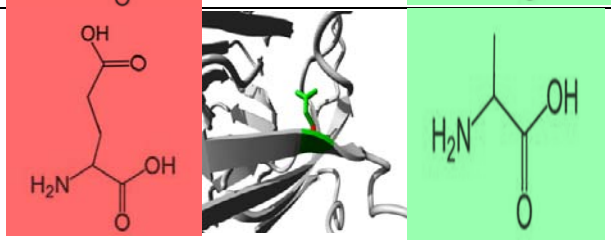
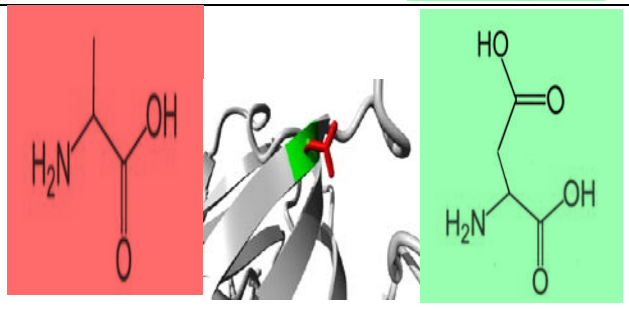
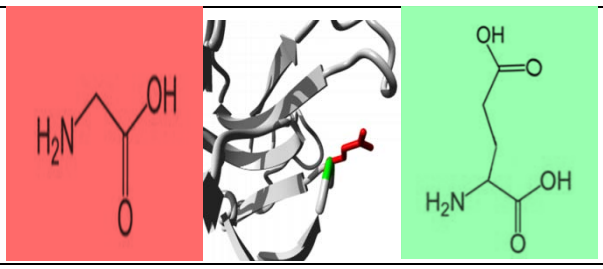
Mutation	SNP & GO Prediction	SNP & GO Probability	SNP & GORI	PHD Prediction	PHD Probability	PHD RI	I-Mutant Prediction	I-Mutant RI
L4D	Neutral	0.363	3	Neutral	0.439	4		
Y6F	Neutral	0.242	5	Disease	0.545	1		
G11E	Neutral	0.339	3	Disease	0.739	5		
G11K	Disease	0.509	0	Disease	0.782	6	Decrease	5
S24I	Neutral	0.036	9	Neutral	0,215	6		
A41D	Disease	0.527	1	Disease	0.876	8	Decrease	7
E42A	Disease	0.645	3	Disease	0.837	7	Decrease	3
R53Q	Disease	0.570	1	Disease	0.862	7	Decrease	9
W60V	Disease	0.623	2	Disease	0.843	7	Decrease	5
W85M	Neutral	0.233	8	Neutral	0.233	5		
P99E	Neutral	0.288	4	Disease	0.548	1		
V113C	Neutral	0.471	1	Disease	0.681	4		
A122F	Neutral	0.477	0	Disease	0.733	5		
G123E	Neutral	0.483	2	Disease	0.884	8		
P158L	Neutral	0.425	1	Disease	0.839	7		

L163F	Neutral	0.376	2	Disease	0.739	5		
E168K	Disease	0.602	2	Disease	0.896	8	Decrease	9
G198D	Disease	0.877	8	Disease	0.948	9	Decrease	8
A293E	Neutral	0.411	2	Disease	0.675	4		
T299A	Neutral	0.298	4	Disease	0.633	3		
R307C	Neutral	0.372	3	Neutral	0.489	0		
V316F	Disease	0.821	6	Disease	0.916	8	Decrease	3
M339I	Disease	0.522	0	Disease	0.813	6	Decrease	7
G360R	Disease	0.734	6	Disease	0.759	5	Decrease	4
P373L	Disease	0.635	3	Disease	0.612	2	Decrease	7

The structural impact of the SNPs on protein structure and function was investigated using Project hope. Eleven which were damaging, disease related and affects the protein stability were analyzed using Project Hope the results were shown in Table (5):

Table (5): The effect mutation on protein sing Project Hope prediction

SNP ID	3D structure	Effect
rs138558042 **Proline** into a **Leucine** at position 373		The damaging effect is due to increased size and conservancy. Prolines are known to have a very rigid structure, mutation changes a proline with such a function into another residue, thereby disturbing the local structure.
rs368717991 **Glycine** into a **Arginine at** position 360		The damaging effect is due to difference in charge the mutation introduces a charge, this can cause repulsion, the mutant residue is bigger, this might lead to bumps. The torsion angles for this residue are unusual mutation into another residue will force the local backbone into an incorrect conformation and will disturb the local structure.
rs139501220 **Methionine** into a **Isoleucine** at position 339		The damaging effect is due to wild-type and mutant amino acids differ in size. The mutant residue is smaller; this might lead to loss of interactions.
rs199927284 **Valine** into a **Phenylalanine** at position 316		The damaging effect is due to, mutant amino acids increase in size leading to the loss of interactions.

rs199536408**Glycine** into a **Aspartic Acid** at position 198		The mutant residue is bigger and probably will not fit. Glycine is flexible enough to make these torsion angles, mutation into another residue will force the local backbone into an incorrect conformation and will disturb the local structure.
rs375283568**Glutamic Acid** into a **Lysine** at position 168		The damaging effect is due to mutant residue is bigger than the wild-type and is locatedin a domain that is important for the main activity of the protein this residue might disturb this function
rs143267384 **Tryptophan** into a **Valine** at position 60		The damaging effect is since, the mutation is found in a conserved region of the protein and important for its activity. The mutant residue is smaller than the wild residue, causing an empty space in the core of the protein.
rs200808744**Arginine** into a **Glutamine at** position 53		The mutant residue is smaller than the wild-type residue. This will cause a possible loss of external interactions. There is also difference in the charge between the wild and mutant type.Mutation of the residue might disturb this function
rs373921680**Glutamic Acid** into a **Alanine** at position 42		Only this residue type was found at this position. The damaging effect is due to decrease of wild-type residue size lead to loss of interactions with other molecules or residues. Decrease hydrophobicity of the mutant residue leading to loss of Hydrophobic interactions.
rs199536408 **Alanine** into a **Aspartic Acid** at position 41		The damage may come from the fact that the mutation is at a highly conserved region. The mutant type is bigger than the wild one. It is also negatively charged while the wild is neutral. The residue is located on the surface of the protein, mutation of this residue can disturb interactions with other molecules or other parts of the protein. The mutation might cause loss of hydrophobic interactions with other molecules on the surface of the protein.
lycine into a **Glutamic Acid at** position 11		The damaging effect is due to mutant residue is bigger and probably will not fit. Glycine is flexible enough to make these torsion angles, mutation into another residue will force the local backbone into an incorrect conformation. charge, this can disrupts the local structure.

**Note Grey colour: protein chains, red colour atoms are the wild amino acid residues, green are the mutated amino acids*

IV. Discussion

AKU is normally characterized through genetic changes in the HGD gene but the identification of variants likely affecting structure is not always straightforward. Evolutionary conservation (Shannon entropy) and population conservation (MTR) scores indicated that AKU variants were located at more conserved residue positions. This could provide insight into novel missense variants that have a high probability of being deleterious (Ascher et al., 2019).

In this study a total of 11 SNPs were shown to be damaging, disease related and affecting the protein stability using 6 different software. Seven of them were novel not reported in ClinVar database. Namely, rs370453859 (G11K), rs199536408 (A41D), rs143267384 (W60V), rs199536408 (G198D), rs199927284 (V316F), rs139501220 (M339I), rs138558042 (P373L). The effect of the mutation on the protein function was due to the location if it is in a conserved region the protein will be highly affected. Most of these mutations were in a conserved region. Also the difference in size between the wild and mutant residue affects the protein function, if the mutant residue is bigger in size (G11K, A41D, G198D, V316F and P373L) it cannot fit and might lead to bumps, if it is smaller (W60V and M339I) this will cause an empty space in the core of the protein. The difference in hydrophobicity will leads to loss of hydrophobic interactions with other molecules on the surface of the protein. The physical properties between the wild and mutant amino acid also affects the protein function (the flexibility of Glycine and the rigidity of Proline).

Compromising the Homogentisate oxidase enzyme function Nemethova et al., 2016 showed that the missense variants are predicted to affect the activity of the enzyme by three molecular mechanisms: decrease of stability of individual protomers, disruption of protomer–protomer interactions or modfication of residues in the active site region. In agreement with our results fournsSNPs namely rs373921680 (E42A), rs200808744 (R53Q), rs375283568 (E168K), and rs368717991 (G360R), have already been previously reported as mutation in HDG gene in patients with AKU through direct DNA sequencing (de Bernabe et al., 1998; Nemethova et al, 2016; Ascher et al., 2019; Vilboux et al., 2009; Higashino, 1998; and Porfirio et al., 2000). According to, de Bernabe et al., 1998,who mentioned that rs373921680 (E42A) is pathogenic and clustered within exon 03, the variant remarks is missense, predicted mutation resulting in the amino acid substitutions affect the protomer destabilization, hexamer disruptionis crucial for the enzymatic activity of HGD. In the study by, Nemethova et al, 2015, they recorded that, SNPsrs200808744 (R53Q) was remarkably changing the amino acid residues and found to be pathogenic, and this mutation has recently been reported as one of the important mutations in this HDG gene, predicted the mutation to be highly destabilize the formation of the hexamer, because of the loss of the interactions made by the arginine. Higashino et al., 1998 approved that, rs375283568 (E168K) as a pathogenic mutation and changed a glutamic acid residue at position 168 to a lysine residue. Predicted mutation affect substitution hexamer disruption. Porfirio et al., 2000, found that, rs368717991 (G360R) affect the protomer destabilization and hexamer disruption due to substitution of wide amino Glycine into an Arginine at position 360. The mutated residue is located in a domain that is important for the main activity of the protein. Mutation of the residue might disturb this function.

These nsSNPs, rs375396766 (P158L) and rs143556739 (R307C) were predicted by other researchers to be pathogenic, in this study they were predicted to be damaging but not disease related.

The structural analysis of the identified variants allowed their classfication based on the predicted effects into three classes: (i) those that alter the active site, reducing activity; (ii) those that destabilize the protein, reducing activity; and (iii) those that prevent formation of the homohexamer, disrupting activity (Nemethova et al, 2016). Stabilizing amino acids can be predicted based on long-range interactions in protein structures and hydrophobicity and conservation of amino acid residues. Mutations found at stability centers were considered by us to be destabilizing and thus deleterious. SRide combines several methods to identify residues expected to play key roles in stabilization. It analyzes tertiary structures, rather than primary structures, and the evolutionary conserved residues contained within. A residue is predicted to be stabilizing if it is surrounded by hydrophobic residues, exhibits long-range order, has a high conservation score, and is part of a stability center (Magyar et al., 2005).

V. Conclusion

The data presented in this study represent extensive computational account of AKU nsSNPs, to filter out deleterious substitutions that are unlikely to affect protein function and can offer a more feasible means for phenotype prediction based on the biochemical severity of the amino acid substitution and the protein sequence and structural information. A total of 423 SNPs were found to be associated with mutations in HGD gene and we identified 7 novel HGD gene variants and associated intragenic polymorphisms, and they provide a general understanding of the variability at the HGD gene locus in both AKU and normal individuals, population genetics and clinical studies are important to confirm the outcomes of such study.

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Global Journal of Medical Research: F
Diseases
Volume 22 Issue 4 Version 1.0 Year 2022
Type: Double Blind Peer Reviewed International Research Journal
Publisher: Global Journals
Online ISSN: 2249-4618 & Print ISSN: 0975-5888

A Brief Study on the Prevalence of Malaria in Kolkata, West Bengal, India

By Aditi Munmun Sengupta, Diptendu Chatterjee & Rima Ghosh

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Abstract- *Objectives:* Malaria has been a major public health problem in India, with cases therein contributing significantly to the overall malaria burden within South East Asia. Majority of malaria cases in India have occurred within the eastern and central regions of the country. Over 80% of the country's total malaria cases have been reported from 10 states. Statistics for the state of West Bengal had reported approximately 26,000 and 25,000 malaria cases in 2014 and 2018, respectively, with Kolkata still being considered the most malaria-prone district of West Bengal.

Methods: A cross-sectional study was designed based on data collected from the Kolkata Municipal Corporation documents on Taltala area residents during the winter. Collected data included age, sex, malaria category, medicine intake history, and others. Outcomes following medication, such as chloroquine tablets, artemisinin-based combination therapies, and primaquine, were also assessed.

Keywords: *control strategies, Malaria, India, Kolkata, Plasmodium vivax, Plasmodium falciparum, seasonal trend.*

GJMR-F Classification: *DDC Code: 614.532 LCC Code: RA644.M2*

Strictly as per the compliance and regulations of:

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Aditi Munmun Sengupta [α], Diptendu Chatterjee [σ] & Rima Ghosh [ρ]

Abstract- Objectives: Malaria has been a major public health problem in India, with cases therein contributing significantly to the overall malaria burden within South East Asia. Majority of malaria cases in India have occurred within the eastern and central regions of the country. Over 80% of the country's total malaria cases have been reported from 10 states. Statistics for the state of West Bengal had reported approximately 26,000 and 25,000 malaria cases in 2014 and 2018, respectively, with Kolkata still being considered the most malaria-prone district of West Bengal.

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Results: A total of 120 patients were included, the vast majority of whom were male (88.3%). Vivax malaria (87.5%; mean age of cases, 37 years) predominated over falciparum malaria (12.5%; mean age of cases, 28 years). Fewer cases occurred in October (49.16%) compared to November (50.83%), suggesting the prevalence of malaria during the winter.

Conclusions: The current study showed that uncomplicated malaria cases predominated. Moreover, severe malaria was infrequent, no fatalities occurred, and response to oral drug therapy was good.

Keywords: control strategies, Malaria, India, Kolkata, Plasmodium vivax, Plasmodium falciparum, seasonal trend.

सार- उद्देश्य: **मलेरिया भारत में एक प्रमुख सार्वजनिक स्वास्थ्य समस्या रही है, इसके मामलों ने दक्षिण पूर्व एशिया के भीतर समग्र मलेरिया बोझ में महत्वपूर्ण योगदान दिया है। भारत में मलेरिया के अधिकांश मामले देश के पूर्वी और मध्य क्षेत्रों में हुए हैं। देश के कुल मलेरिया के 80% से अधिक मामले 10 राज्यों से सामने आए हैं। पश्चिम बंगाल राज्य के आंकड़ों में क्रमशः 2014 और 2018 में लगभग 26,000 और 25,000 मलेरिया के मामले दर्ज किए गए थे, कोलकाता को अभी भी पश्चिम बंगाल का सबसे अधिक मलेरिया-प्रवण जिला माना जाता है।**

तरीके: **सर्दियों के दौरान तलतला क्षेत्र के निवासियों पर कोलकाता नगर निगम के दस्तावेजों से एकत्र किए गए आंकड़ों के आधार पर एक क्रॉस-सेक्शनल अध्ययन तैयार किया गया था। एकत्रित डेटा में आयु, लिंग, मलेरिया श्रेणी, दवा सेवन इतिहास और अन्य शामिल थे। दवा के बाद के परिणामों, जैसे क्लोरोक्वीन की गोलियां, आर्टीमिसिनिन-आधारित संयोजन चिकित्सा और प्राइमाक्वीन का भी मूल्यांकन किया गया था।**

परिणाम: **कुल 120 रोगियों को शामिल किया गया, जिनमें से अधिकांश पुरुष (88.3%) थे। विवैक्स मलेरिया (87.5%; मामलों की औसत आयु, 37 वर्ष) फाल्सीपेरम मलेरिया (12.5%; मामलों की औसत आयु, 28 वर्ष) पर हावी है। नवंबर (50.83%) की तुलना में अक्टूबर (49.16%) में कम मामले सामने आए, जो सर्दियों के दौरान मलेरिया के प्रसार को दर्शाता है।**

निष्कर्ष: **वर्तमान अध्ययन से पता चला है कि मलेरिया के जटिल मामले प्रमुख हैं। इसके अलावा, गंभीर मलेरिया दुर्लभ था, कोई मौत नहीं हुई, और मौखिक दवा चिकित्सा की प्रतिक्रिया अच्छी थी।**

मुख्य शब्द: नियंत्रण रणनीतियाँ, मलेरिया, भारत, कोलकाता, प्लास्मोडियम विवैक्स, प्लास्मोडियम फाल्सीपेरम, मौसमी प्रवृत्ति.

I. Introduction

Malaria has remained a major public health problem in India, with cases therein contributing significantly to the overall malaria burden in Southeast Asia. Majority of malaria cases in India have occurred within the eastern and central regions of the country. Around 90 countries, accounting for approximately 36% of the total world population, continue to be exposed to the risk of malaria. The main causative agent for this infectious disease is a parasite called "*Plasmodium*" from the protozoan family, which is spread through Anopheles or Culex mosquitoes—the main vectors of this infectious disease. World Health Organization (WHO) estimates show that out of the 1.4 billion total population across 11 countries, approximately 1.2 billion are at risk of being exposed to the malaria epidemic. Among the aforementioned 11 countries, India has reported 2.5 million cases of malaria, which accounts for approximately 76% of the total reported cases, substantially contributing to the global burden nowadays,[1,2]. Three prospective research areas can be utilized to study malaria, that is, biological, ecological, and socio cultural. The biological area, in which most studies have focused, holds more significance compared to the rest of other areas [3]. Nonetheless, sociocultural factors are evidently critical in controlling malaria given that human behavior can control the etiology of this disease. The combined interdisciplinary approach has been considered the best possible method of dealing with malaria. Most of the studies in India have focused on prevalence data collected from epidemic investigations. Despite studies

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on malaria, limited data have been available specifically for age, gender, and seasonal variance [4]. The current study therefore focuses on some of these aspects.

a) Background of the study

After India attained independence in 1947, 75 million malaria cases had been estimated in a population of 330 million. During the eradication era in the late 1950s and early 1960s, remarkable malaria eradication had been achievement, with malaria cases significantly declining to just 100,000 cases in 1964. Unfortunately, the number of cases gradually increased thereafter, reaching 6.4 million by 1976 [5]. Nonetheless, despite having the highest burden of malaria within the Southeast Asian region, India has shown a declining trend in malaria incidence in recent years [2]. Malaria is essentially a protozoan infectious disease caused by four main Plasmodium species in humans, namely *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. Among the aforementioned protozoans, *P. vivax* has caused majority of the deaths worldwide. Only female anopheles mosquitoes can be the vector for malaria. In terms of malaria transmission, approximately 30 out of over 400 different species can transmit malaria. Such mosquitoes mostly bite at night, with some resting outdoors and others indoors. A person bitten by a mosquito carrying the malaria parasite may become infected with malaria. Similarly, a mosquito without the malaria parasite who bites a person already infected with malaria may acquire the malaria parasite and subsequently infect another person [6]. The epidemiology of malaria in India is complex given the geo-ecological diversity, multiethnicity, and wide distribution of nine anopheline vectors transmitting three main Plasmodium species: *P. falciparum*, *P. vivax*, and *P. malariae*. The number of cases within the country still account for 6% of global malaria cases and approximately half of the total *Plasmodium vivax* cases worldwide [7]. Kolkata (formerly Calcutta), the capital of state West Bengal, India with an area of 205 km^2, is under the jurisdiction of the Kolkata Municipal Corporation (KMC). According to 2011 census, Kolkata has a population of 45 lakhs. Kolkata has still been considered the most malaria-prone district of West Bengal, India given the conducive climatic condition and urban lifestyle maintained within the city. Over a century ago, the city provided Sir Ronald Ross an opportunity to eradicate the transmission cycle of the disease. Unfortunately, the transmission cycle of malaria has still yet to be interrupted permanently [8]. Nonetheless, the status of malaria within Kolkata has improved considerably over last decade under the keen supervision of the officials of the KMC [9].

b) Objective

The current study aimed to investigate the present status and trends of malaria in a designated ward under the jurisdiction of the KMC to determine timing, location, and distribution of malaria cases, as well as identify risk factors to mitigate future outbreaks.

II. Materials and Methods

A cross-sectional study was designed based on data collected from the KMC documents and a pretested questionnaire administered to Taltala area residents during the winter. For ethical consideration, verbal or written approval was taken from the residents. Variables taken into account included age, sex, malaria category, medicine intake history, and others. Most of the wards were also found to be at high risk for malaria peaking during the postmonsoon season. Appropriate statistics had been utilized for the present study. The study included a total of 120 participants who were interviewed using pretested questionnaires on socio–demographic parameters, education, occupation, household information, and malaria-related behavior upon recruitment. A medical history was taken, after which a clinical examination was performed in all patients using standard protocol. Weight and height were measured following the standard anthropometric protocol. Body mass index was calculated as kg/m^2. Fever was defined as an axillary temperature ≥37.5 °C. Venous blood was collected in ethylenediaminete-traacetic acid vials. Malaria parasites were counted per 200 white blood cells on Giemsa-stained thick blood films, whereas parasite species were defined based on thin-film microscopy.

III. Results

Table 1: Kolkata Municipal Corporation showing indicators of malaria intervention

Borough	ABER	SPR	API
6	9.61	15.6	15.53

ABER, annual blood examination rate; SPR, slide positivity rate; API, annual parasite incidence.

Table 2: Distribution of malaria category

Groups	N = 120	Percentage (%)
Plasmodium vivax (PV)	105	87.5
Plasmodium falciparum (PF)	15	12.5

Table 3: Distribution of subjects according to sex

Sl No.	Groups	N = 120	Percentage (%)
1.	Male	106	88.33
2.	Female	14	11.66

Table 4: Mean and standard deviation (SD) of age among affected individuals

	Plasmodium vivax affected = 105 Mean (SD)	*Plasmodium falciparum* affected = 15 Mean (SD)
Age in years	36.773 (3.59)	28.46 (7.35)

Table 5: Affected population month wise

Sl No.	Characteristics	N = 120	Percentage (%)
1.	October, 2019	59	49.16
2.	November, 2019	61	50.83

Table 6: Treatment procedures

Chloroquine tablets		Artemisinin-based combination therapy	Primaquine tablets	
Total dose: 25 mg/kg given over 3 days. Day 1: 10 mg/kg, followed by 5 mg/kg 6–8 h later. Days 2 and 3: 5 mg/kg in a single dose.	Days 1 and 2: 10 mg/kg. Day 3: 5 mg/kg.	Day 1: 25 mg/kg followed by Day 2 and 3: 12.5 mg/kg	0.25 mg/kg or 15 mg daily for 14 days	0.75 mg/kg weekly for 8 weeks
92 individuals 76.66%	15 individuals 12.5%	7 individuals 5.83%	20 individuals 16.66%	95 individuals 79.16%

Table 1 shows indicators of malaria intervention, including annual blood examination rate, slide positivity rate, and annual parasite incidence among the study participants. A total of 105 (87.5%) individuals were infected with *P. vivax*, while 15 (12.5%) were infected with *P. falciparum* (Table 2). Among the included patients, 106 (88.33%) and 14 (11.66%) were male and female, respectively (Table 3). Moreover, those infected with *P. vivax* and *P. falciparum* had a mean (standard deviation) age of 36.77 (3.59) and 28.46 (7.35) years, respectively (Table 4). Among the included patients, 59 (49.16%) and 61 (50.83%) were infected in October and November, 2019 respectively (Table 5). Table 6 details the patient's antimalarial treatment as recommended by the WHO doses of chloroquine, artemisinin-based combination therapy (ACT), and primaquine. We observed that patients fared better with chloroquine (total dose of 25 mg/kg body weight) distributed over 3 days (76.66%) compared to distributed doses (12.5%). The 3 day treatment with ACT was found to be effective only in a small number of patients (5.83%). Radical treatment with primaquine (0.25 mg/kg or 15 mg daily for 14 days followed by standard chloroquine therapy) yielded a cure rate of 16.66%, whereas a dose of 0.75 mg/kg weekly for 8 weeks yielded a cure rate of 79.16% in affected individuals.

IV. Discussion

The present study showed that among the included patients affected by malaria in Kolkata, almost 88% were due to *P.vivax*, whereas only 15% were due to *P. falciparum*. Majority of the patients managed with oral medications. Moreover, severe malaria was rare, whereas fatalities were absent. The present study has several limitations that need to be considered. The study area selected was mainly populated by individuals from middle or low socioeconomic background. This pattern may in turn impact the knowledge and awareness of malaria, as well as the degree and pace of health care utilization adopted by the private sectors of the city as a whole. However, the present study provides a sufficiently representative depiction of the status of malaria within Kolkata. The percentage of subjects affected by malaria after the peak monsoon season during the early winter months was quite high, suggesting *P. vivax* relapse (i.e., long and short latency) in the eastern part of India. However, given that the present study does not comprehensive investigate this phenomenon, further detailed studies on the matter should be encouraged. The medications adopted from the WHO manual of drugs used in parasitic diseases, 2nd edition [10] has provided the necessary information for understanding routine treatment approaches for

cure. In practice, however, the selection of treatment is influenced not only by the intrinsic properties of the drug but also by the degree to which the locally occurring parasites developed specific patterns of drug resistance. This study emphasized that prompt diagnosis and treatment of the disease is dependent on targeted use of antimalarial drugs with the aim of reducing the risk of drug resistance and unnecessary drug-induced toxicity. The present study did not investigate occurrence of drug-induced toxicity from the antimalarials used or a detailed description of the intrinsic properties of specific drugs and the degree to which locally occurring parasites developed specific patterns of drug resistance to each medication. A number of well-structured National Disease Control/Elimination Programs have been implemented by the state governments following national policies. The organized National Vector Borne Disease Control Program (NVBDCP) provides technical and operational guidelines to the state governments aside from shouldering half the costs for malaria control. Early detection and complete treatment, selective vector control, and behavior change communication are the key components of current malaria control strategies employed by the NVBDCP. To emphasize such components, the present study was conducted in one of the malaria-infested areas within Kolkata, a state of West Bengal. Accordingly, young males of low socioeconomic status, many of whom had migrated from other parts of India, were predominantly affected by malaria. A large percentage of malaria cases occur among individuals of economically productive ages. Determining the actual disease burden and its control is therefore critical in addressing issues regarding effective interventions, with the ultimate aim of lifting human resource above the poverty line. In this regard, strengthening health care systems remain a cornerstone for successful malaria control strategies.

V. Conclusion

To develop the potential of human resource, which is important for equitable and sustained economic growth, malaria control is vital. Therefore, investing in malaria control provides public health benefits while improving the economic environment during the ongoing economic liberalization throughout India.

Acknowledgments: We are grateful to the officials of the Kolkata Municipal Corporation, all study participants, the Department of Anthropology, University of Calcutta, the Department of Physiology, University of Calcutta.

Disclaimer: The findings and conclusions in this report are those of the authors and do not represent the official position of the Kolkata Municipal Corporation.

Financial Assistance: Financial assistance was received from UPE 2, while a research grant and teachers' research grant were received from the University of Calcutta.

Disclosures: AMS: conceptualization of the study, literature search, preparation of the first draft and critical revision of the manuscript; DC: conceptualization of the study, revision of the manuscript; RS: literature search, data collection.

Conflicts of interest: The authors declare no conflicts of interest.

Editorial assistance: Enago (www.enago.com) contributed in the English language review and provided editorial assistance for this paper

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Authorship Policies

Global Journals follows the definition of authorship set up by the Open Association of Research Society, USA. According to its guidelines, authorship criteria must be based on:

1. Substantial contributions to the conception and acquisition of data, analysis, and interpretation of findings.
2. Drafting the paper and revising it critically regarding important academic content.
3. Final approval of the version of the paper to be published.

Changes in Authorship

The corresponding author should mention the name and complete details of all co-authors during submission and in manuscript. We support addition, rearrangement, manipulation, and deletions in authors list till the early view publication of the journal. We expect that corresponding author will notify all co-authors of submission. We follow COPE guidelines for changes in authorship.

Copyright

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Appealing Decisions

Unless specified in the notification, the Editorial Board's decision on publication of the paper is final and cannot be appealed before making the major change in the manuscript.

Acknowledgments

Contributors to the research other than authors credited should be mentioned in Acknowledgments. The source of funding for the research can be included. Suppliers of resources may be mentioned along with their addresses.

Declaration of funding sources

Global Journals is in partnership with various universities, laboratories, and other institutions worldwide in the research domain. Authors are requested to disclose their source of funding during every stage of their research, such as making analysis, performing laboratory operations, computing data, and using institutional resources, from writing an article to its submission. This will also help authors to get reimbursements by requesting an open access publication letter from Global Journals and submitting to the respective funding source.

Preparing your Manuscript

Authors can submit papers and articles in an acceptable file format: MS Word (doc, docx), LaTeX (.tex, .zip or .rar including all of your files), Adobe PDF (.pdf), rich text format (.rtf), simple text document (.txt), Open Document Text (.odt), and Apple Pages (.pages). Our professional layout editors will format the entire paper according to our official guidelines. This is one of the highlights of publishing with Global Journals—authors should not be concerned about the formatting of their paper. Global Journals accepts articles and manuscripts in every major language, be it Spanish, Chinese, Japanese, Portuguese, Russian, French, German, Dutch, Italian, Greek, or any other national language, but the title, subtitle, and abstract should be in English. This will facilitate indexing and the pre-peer review process.

The following is the official style and template developed for publication of a research paper. Authors are not required to follow this style during the submission of the paper. It is just for reference purposes.

Manuscript Style Instruction (Optional)

- Microsoft Word Document Setting Instructions.
- Font type of all text should be Swis721 Lt BT.
- Page size: 8.27" x 11'", left margin: 0.65, right margin: 0.65, bottom margin: 0.75.
- Paper title should be in one column of font size 24.
- Author name in font size of 11 in one column.
- Abstract: font size 9 with the word "Abstract" in bold italics.
- Main text: font size 10 with two justified columns.
- Two columns with equal column width of 3.38 and spacing of 0.2.
- First character must be three lines drop-capped.
- The paragraph before spacing of 1 pt and after of 0 pt.
- Line spacing of 1 pt.
- Large images must be in one column.
- The names of first main headings (Heading 1) must be in Roman font, capital letters, and font size of 10.
- The names of second main headings (Heading 2) must not include numbers and must be in italics with a font size of 10.

Structure and Format of Manuscript

The recommended size of an original research paper is under 15,000 words and review papers under 7,000 words. Research articles should be less than 10,000 words. Research papers are usually longer than review papers. Review papers are reports of significant research (typically less than 7,000 words, including tables, figures, and references)

A research paper must include:

a) A title which should be relevant to the theme of the paper.
b) A summary, known as an abstract (less than 150 words), containing the major results and conclusions.
c) Up to 10 keywords that precisely identify the paper's subject, purpose, and focus.
d) An introduction, giving fundamental background objectives.
e) Resources and techniques with sufficient complete experimental details (wherever possible by reference) to permit repetition, sources of information must be given, and numerical methods must be specified by reference.
f) Results which should be presented concisely by well-designed tables and figures.
g) Suitable statistical data should also be given.
h) All data must have been gathered with attention to numerical detail in the planning stage.

Design has been recognized to be essential to experiments for a considerable time, and the editor has decided that any paper that appears not to have adequate numerical treatments of the data will be returned unrefereed.

i) Discussion should cover implications and consequences and not just recapitulate the results; conclusions should also be summarized.
j) There should be brief acknowledgments.
k) There ought to be references in the conventional format. Global Journals recommends APA format.

Authors should carefully consider the preparation of papers to ensure that they communicate effectively. Papers are much more likely to be accepted if they are carefully designed and laid out, contain few or no errors, are summarizing, and follow instructions. They will also be published with much fewer delays than those that require much technical and editorial correction.

The Editorial Board reserves the right to make literary corrections and suggestions to improve brevity.

Format Structure

It is necessary that authors take care in submitting a manuscript that is written in simple language and adheres to published guidelines.

All manuscripts submitted to Global Journals should include:

Title

The title page must carry an informative title that reflects the content, a running title (less than 45 characters together with spaces), names of the authors and co-authors, and the place(s) where the work was carried out.

Author details

The full postal address of any related author(s) must be specified.

Abstract

The abstract is the foundation of the research paper. It should be clear and concise and must contain the objective of the paper and inferences drawn. It is advised to not include big mathematical equations or complicated jargon.

Many researchers searching for information online will use search engines such as Google, Yahoo or others. By optimizing your paper for search engines, you will amplify the chance of someone finding it. In turn, this will make it more likely to be viewed and cited in further works. Global Journals has compiled these guidelines to facilitate you to maximize the web-friendliness of the most public part of your paper.

Keywords

A major lynchpin of research work for the writing of research papers is the keyword search, which one will employ to find both library and internet resources. Up to eleven keywords or very brief phrases have to be given to help data retrieval, mining, and indexing.

One must be persistent and creative in using keywords. An effective keyword search requires a strategy: planning of a list of possible keywords and phrases to try.

Choice of the main keywords is the first tool of writing a research paper. Research paper writing is an art. Keyword search should be as strategic as possible.

One should start brainstorming lists of potential keywords before even beginning searching. Think about the most important concepts related to research work. Ask, “What words would a source have to include to be truly valuable in a research paper?” Then consider synonyms for the important words.

It may take the discovery of only one important paper to steer in the right keyword direction because, in most databases, the keywords under which a research paper is abstracted are listed with the paper.

Numerical Methods

Numerical methods used should be transparent and, where appropriate, supported by references.

Abbreviations

Authors must list all the abbreviations used in the paper at the end of the paper or in a separate table before using them.

Formulas and equations

Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

The Administration Rules

Administration Rules to Be Strictly Followed before Submitting Your Research Paper to Global Journals Inc.

Please read the following rules and regulations carefully before submitting your research paper to Global Journals Inc. to avoid rejection.

Segment draft and final research paper: You have to strictly follow the template of a research paper, failing which your paper may get rejected. You are expected to write each part of the paper wholly on your own. The peer reviewers need to identify your own perspective of the concepts in your own terms. Please do not extract straight from any other source, and do not rephrase someone else's analysis. Do not allow anyone else to proofread your manuscript.

Written material: You may discuss this with your guides and key sources. Do not copy anyone else's paper, even if this is only imitation, otherwise it will be rejected on the grounds of plagiarism, which is illegal. Various methods to avoid plagiarism are strictly applied by us to every paper, and, if found guilty, you may be blacklisted, which could affect your career adversely. To guard yourself and others from possible illegal use, please do not permit anyone to use or even read your paper and file.

Criterion for Grading a Research Paper (Compilation) by Global Journals

Please note that following table is only a Grading of "Paper Compilation" and not on "Performed/Stated Research" whose grading solely depends on Individual Assigned Peer Reviewer and Editorial Board Member. These can be available only on request and after decision of Paper. This report will be the property of Global Journals.

Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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ISSN 9755896