Diabetes and hypertension in patients with psoriasis: a cross sectional and case control study in a tertiary care hospital of Bangladesh

Samira Jamal1*, Sheikh Anwarul Karim2, Sheikh Mahee Ridwan Raihan3, Rajat Biswas4, Mansurul Alam1

1Department of Dermatology, Chittagong Medical College, Chittagong, Bangladesh
2Department of Endocrinology, Sylhet MAG Osmani Medical College, Sylhet, Bangladesh
3College of Arts and Sciences, University of North Carolina Greensboro, USA
4Chattogram Maa-O-Shishu Hospital Medical College, Chittagong, Bangladesh

ABSTRACT

Background: In this study our main goal was to evaluate the association of psoriasis as a risk predictor for the occurrence of diabetes mellitus (DM) and hypertension (HTN).

Methods: This case control study was carried out in the department of dermatology and venereology, Chittagong medical college hospital (CMCH), Chittagong, Bangladesh from 15 June 2011 to 14 May 2012. Where 60 patients with psoriasis and 60 patients with skin diseases other than psoriasis were included according to availability within the study period.

Results: During study, among the psoriatic patients, most of the patients with DM and HTN had body mass index (BMI) within normal limit. During analysis of different clinical findings in psoriatic patients scaling was present in all the cases followed by Auspitz sign, koebnerization, itching, scalp involvement and nail changes. Patients with psoriasis were found to have higher incidence of DM and HTN in comparison to their non-psoriatic control group. It was also observed that psoriatic patients having DM and HTN had longer duration of diseases (p<0.05).

Conclusions: In conclusion, our study indicates that patients with psoriasis have an increased risk of DM and HTN, confirming the findings from previous several case control and cross sectional studies. These data illustrate the importance of considering psoriasis as a systemic disorder rather than simply a skin disease. Awareness of concurrent diseases will provide the clinician an opportunity of screening for others systemic diseases.

Keywords: Psoriasis, Diabetes, Hypertension
exposures. Clinically psoriasis is characterized by circumscribed, erythematous, dry scaling plaques of various sizes covered by silvery white lamellar scales.

There are five main types of psoriasis: chronic plaque psoriasis, guttate psoriasis, inverse psoriasis, pustular psoriasis, erythrodermic psoriasis. Among these types, pustular and erythrodermic variant are commonly flare up, must seek medical attention and to be hospitalized immediately because these conditions can lead to severe illness.

Inflammation is a risk factor for high blood pressure and may also contribute to insulin resistance, a pre diabetic stage where body does not respond to the glucose regulating hormone insulin. Systemic inflammation in psoriasis and an increased prevalence of unhealthy life style factors have been independently associated with insulin resistance and unfavourable cardiovascular risk profile. In case of such an extended inflammation it is conceivable also to assume systemic consequences. Most health care providers including dermatologists do not associate psoriasis with an unfavourable cardiovascular risk profile, but more and more evidence is emerging that might be the case. Alternatively, steroid therapy either topical or systemic and other treatments for psoriasis may promote development of DM or HTN. In this study our main goal was to evaluate the association psoriasis as a risk predictor for occurrence of DM and HTN.

**Objective**

The objective was to assess the association of psoriasis as a risk predictor for the occurrence of DM and HTN.

**METHODS**

**Type of study**

This study was a case control study.

**Place of study**

This study was carried out in department of dermatology and venereology, CMCH, Chittagong from 15 June 2011 to 14 May 2012.

**Study population**

Patients presented with psoriasis and presented with skin problem other than psoriasis were the study population.

**Sampling technique**

The sampling technique was purposive/judgment sampling.

**Sample size**

Assuming the prevalence of DM and HTN among the psoriasis patients was 35% and acceptable error was 10% of it (prevalence), we got required sample size,

\[
 n = \frac{Z^2 \times p \times q}{E^2}
\]

where,

\[ Z = \text{standard normal deviation} = 1.96 \],
\[ p = \text{prevalence (assumed) of the disease}, \]
\[ q = 1 - p = 0.65 \],
\[ E = \text{acceptable error} = 10\% \text{ of } p = 0.035 \],

So,

\[
 n = \frac{(1.96)^2 \times 0.35 \times 0.65}{0.035^2} = 713.44.
\]

According to above formula, sample size was obtained but due to time limitation, in the present study 60 patients with psoriasis and 60 patient with skin disease other than psoriasis were included according to availability within study period.

**Selection criteria**

**Inclusion criteria**

*For cases*: diagnosed case of psoriasis, patients of both sexes age group 18-65 years were included as cases.

*For control*: patients without psoriasis and age matched patients for cases were included as control.

**Exclusion criteria**

Patients with pregnancy, secondary causes of DM, Cushing syndrome, acromegaly, thyrotoxicosis, pancreatitis, Ca-pancreas were excluded from the study. Patients intaking drugs like corticosteroid, thiazide diuretics were excluded. Secondary causes of HTN like Cushing syndrome, thyroid disorders, acromegaly chronic kidney disease (CKD) drugs like corticosteroid, OCP (oral contraceptive pill) were also excluded. Patients unwilling to give consent or severely ill patient like patients with renal failure, myocardial infarction shock were excluded from the study.

**Study procedure**

Patients attending in the dermatology department were diagnosed case or psoriasis was included in the study. 60 patients with age matched control who were attending in the same department with skin problem were also
selected. These patients were selected after excluding the exclusion criteria. Psoriasis was diagnosed clinically attending in the dermatology outpatient department of CMCH. Secondary causes of DM and HTN were also excluded clinically. Selected patients were informed about the aims, objectives, significance and detail procedure of the study before examination. An informed written consent was taken from all the patients who were selected for the study and encouraged for voluntary participation and allowed freedom to withdraw from the study whenever they liked even after participation. All eligible subjects were provided a structured questionnaire with direct supervision by the researcher herself to obtain socio-demographic and health related. Then clinical examination was done. Blood pressure was recorded by a standard sphygmomanometer in sitting position after 30 minutes rest. At least two recordings of blood pressure of the patient were taken on two occasions. Then average blood pressure was noted. Patients were asked to come in fasting condition for at least 8 to 12 hours. Fasting blood sample was taken for fasting blood sugar and fasting lipid profile. Then patients were given 75 gm glucose mixed in 300 ml of plain water. After two hours second blood sample was also collected for post prandial blood sugar. Blood sample was collected by same laboratory technician and analysis was done in the clinical pathology department of CMCH.

**Data collection method**

All relevant information for each individual study subject was recorded on pre-tested data sheet. The data sheet was used for collection of information. Data was collected by the researcher.

**Data processing plan**

Data was processed and analyzed using computer software SPSS (statistical packages for social sciences version-19). The test statistics was used for analysis of data are student’s t test (for comparison of data presented in quantitative scale like blood glucose level), Chi square test (for comparison of data presented in categorical scale like presence of DM and HTN in two groups). For any analytical test, the level of significance is 0.05 and p value <0.05 was considered significant.

**Ethical approval**

Ethical approval was taken from CMCH.

**RESULTS**

Table 1 shows that among the total study subjects half of the patients included with diagnosed case of psoriasis and the other half were with skin diseases other than psoriasis.

In Table 2 shows socio-demographic status of patients. Among the study subject, two third was male. There was no significant difference in sex between group A and group B. In group A most of the patients belong to 4th decade and in group B was equal distribution of age group between 30-60 years.

In Table 3 shows personal histories among the study group where among the psoriasis patients, family history of psoriasis was present among 30% of the patients.

In Table 4 shows distribution of patients in relation with BMI grading and DM and HTN among the psoriatic patients. Most of the patients with DM/HTN had BMI within normal limit.

In Figure 1 shows clinical findings of the patients with psoriasis. Regarding analysis of different clinical findings in psoriatic patients scaling was present in all the cases followed by Auspitz sign, koebnerization, itching, scalp involvement and nail change.

In Table 5 shows distribution of patients in relation with duration of illness with DM/HTN. Among the psoriatic patients having DM/HTN had longer duration of diseases (p<0.05).

Table 6 shows distribution of duration of illness grading among the study group A with X² test significance. Where 34.2% cases patients had HTN/DM with 6-10 years duration of psoriasis. Followed by 22.9% cases patients had HTN/DM with ≤5 years duration of psoriasis, 20% cases had HTN/DM with 11-15 years duration of psoriasis, 8.6% cases patients had HTN/DM with 16-20 years duration of psoriasis, 5.7% cases patients had HTN/DM with 21-25 years and 26-30 years duration of psoriasis and 2.9% cases patients had HTN/DM with >30 years duration of psoriasis.

Table 7 showed on analysis of different clinical findings in psoriatic patients scaling was present in almost all the cases followed by Auspitz sign, koebnerization, itching, scalp involvement and nail changes and others.

Table 8 showed significant differences in systolic and diastolic blood pressure between the two study groups (group A patients with psoriasis and group B patients without psoriasis).

Table 9 showed significant differences in fasting and post prandial blood glucose levels between the two study groups (group A patients with psoriasis and group B patients without psoriasis at p≤0.005 levels).

Among the study subjects DM was found in 26 patients in group A and 10 in group B patients (OR (CI)=3.824), HTN was found in 23 patients in group A and 8 in group B patients (OR(CI)=4.041).
Table 1: Distribution of study groups (N=120).

| Study groups                  | Frequency | Percentage |
|------------------------------|-----------|------------|
| Group A (with psoriasis)     | 60        | 50         |
| Group B (without psoriasis)  | 60        | 50         |
| Total                        | 120       | 100        |

Table 2: Sociodemographic status of patients.

| Variables          | Study group          |          |          | X² test of significance |
|--------------------|----------------------|----------|----------|-------------------------|
|                    | Group A | Group B |          |                         |
| Sex                |          |         |          |                         |
| Male               | 40   | 72     | 53.3     | NS=not significant (p>0.05) |
| Female             | 20   | 48     | 46.7     |                         |
| Age group (in years) |          |         |          |                         |
| ≤30                | 6    | 20     | 23.3     |                         |
| 31-40              | 8    | 21     | 21.7     |                         |
| 41-50              | 24   | 38     | 23.3     |                         |
| 51-60              | 18   | 33     | 25.0     |                         |
| >60                | 4    | 8      | 6.7      |                         |
| Age (in years)     |          |         |          |                         |
| Groups name        |          | Mean ±SD | Median  |                         |
| Number             | 60 | 47.78 ± 9.81 | 48 |                         |
| Number             | 60 | 44.97 ± 11.86 | 47 |                         |
| Total              | 120 | 46.38 ± 10.93 | 48 |                         |
| X² test of significance |         |          |          |                         |
| P=0.136NS          |         |          |          |                         |
| P=0.121NS          |         |          |          |                         |
| P=0.159NS          |         |          |          |                         |

Table 3: Personal histories among the study group.

| Study group                  | Frequency | % |
|------------------------------|-----------|---|
| Family history of psoriasis  |           |   |
| Present                      | 18        | 30|
| Absent                       | 42        | 70|
| Occupational history         |           |   |
| Service holder               | 21        | 35|
| House wife                   | 18        | 30|
| Businessman                  | 13        | 21.7|
| Farmer                       | 8         | 13.3|

Table 4: Distribution of patients in relation with BMI grading and DM and HTN.

| BMI grading (kg/m²) | Study group A | |          | Total | X² test significance |
|---------------------|---------------|----------|----------|----------------------|-------------------------|
|                     | With HTN/DM | Without HTN/DM | | Number | % | Number | % | Number | % |                             |
| <18.5               | 0           | 1         | 1        | 0    | 0 | 1     | 1 | 1 | 1.7 |                             |
| 18.5-24.9           | 23          | 21        | 44       | 44   | 73.3 |                  |
| 25.0-29.9           | 11          | 12        | 60       | 60   | 100 |                  |
| ≥30.0               | 1           | 0         | 1        | 1    | 1.7 |                  |
| Total               | 35          | 25        | 60       | 60   | 100 |                  |

Table 5: Distribution of patients in relation with duration of illness with DM/HTN.

| Duration illness (in years) | N | Mean ±SD | Significance |
|-----------------------------|---|----------|--------------|
| With HTN/DM                 | 35 | 12.31 ± 8.45 | P=0.041 |
| Without HTN/DM              | 25 | 8.60 ± 5.28 |            |
| Total                       | 60 | 10.77 ± 7.48 |            |
Table 6: Distribution of duration of illness grading among the study group a with X² test significance.

| Duration of illness (in years) | Study group A |  | X² test of significance |
|-------------------------------|---------------|------------------|---------------------------|
|                               | With HTN/DM   | Without HTN/DM   | Total                     | P=0.774 NS |
| ≤5                            | 8             | 8                | 16                        | 26.7       |
| 6-10                          | 12            | 110              | 22                        | 36.6       |
| 11-15                         | 7             | 5                | 12                        | 20         |
| 16-20                         | 3             | 1                | 4                         | 6.7        |
| 21-25                         | 2             | 5                | 3                         | 5          |
| 26-30                         | 2             | 0                | 2                         | 3.3        |
| >30                           | 1             | 0                | 1                         | 1.7        |
| Total                         | 35            | 100              | 60                        | 100        |

Table 7: Distribution of positive clinical findings among the study group A.

| Clinical findings                | Frequency | Percentage (%) |
|----------------------------------|-----------|----------------|
| Scaling                          | 60        | 100            |
| Itching                          | 39        | 65             |
| Auspitz sign                     | 47        | 78.3           |
| Koebnerization                   | 43        | 71.7           |
| Scalp involvement                | 36        | 60             |
| Hair change                      | 4         | 6.7            |
| Nail change                      | 29        | 48.3           |
| Mucous membrane lesion           | 0         | 0.0            |
| Leg oedema                       | 2         | 3.3            |
| Urine albumin                    | 20        | 33.3           |
| Cardiomegaly on chest X-ray      | 11        | 18.3           |

Table 8: Blood pressure among the study group (with t test of significance).

| Blood pressure        | Number | Mean ±SD | Median | Range | Significance |
|-----------------------|--------|----------|--------|-------|--------------|
| Systolic (in mmhg)    |        |          |        |       |              |
| Group A               | 60     | 130.08 ±18.42 | 130   | 100-210 | P=0.002 highly significant |
| Group B               | 60     | 120.50 ±13.74 | 120   | 100-140 |
| Total                 | 120    | 125.29 ±16.88 | 130   | 100-210 |
| Diastolic (in mmhg)   |        |          |        |       |              |
| Group A               | 60     | 82.67 ±7.04  | 80    | 75-100  | P=0.007 highly significant |
| Group B               | 60     | 78.50 ±9.31  | 80    | 60-100  |
| Total                 | 120    | 80.58 ±8.48  | 80    | 60-100  |

Table 9: Fasting and post prandial blood sugar between the study groups (with t test of significance).

| Blood glucose          | Groups | Number | Mean ±SD | Median | Range | Level of significance |
|------------------------|--------|--------|----------|--------|-------|-----------------------|
| Fasting plasma glucose |        |        |          |        |       |                       |
| Group A                | 60     | 102.53 ±27.67 | 95.00 | 70-190  | P=0.011 significant |
| Group B                | 60     | 92.00 ±15.37  | 89.50 | 68-138  |
| Total                  | 120    | 97.27 ±22.90  | 90.00 | 68-190  |
| Post prandial plasma glucose |        |        |          |        |       |                       |
| Group A                | 60     | 144.75 ±49.98 | 130.00| 90-360  | P=0.019 significant |
| Group B                | 60     | 127.20 ±27.27 | 124.00| 85-198  |
| Total                  | 120    | 135.97 ±41.04 | 126.00| 85-360  |

Table 10: Distribution of associated illness between the study groups (with X² test of significance N=120).

| Associated illness | Study groups |  | X² test of significance |
|-------------------|--------------|-------------------|--------------------------|
|                   | Group A      | Group B           | Total                    | P=0.001 NS |
| Diabetes mellitus | 26           | 10                | 36                       | 30          |

Continued.
The present study was done among the 120 psoriatic and non-psoriatic patients to evaluate the risk of DM and HTN. It was done in the dermatology and venereology department of CMCH. This study included 60 patients of diagnosed case of psoriasis and 60 patients of skin disease other than psoriasis after excluding the exclusion criteria. Psoriatic patients are diagnosed clinically attending in the CMCH. Secondary causes of DM and HTN are excluded clinically. Among 60 psoriasis patients, those having DM and HTN had longer duration of the disease (psoriasis). Initially they were diagnosed as a psoriasis then developed DM and HTN. A number of drugs have been reported to precipitate or exacerbate psoriasis in different case reports and case series. Other drugs reported as potential risk factors for psoriasis include antibiotics, lithium, antihypertensive agent (beta blocking agents, angiotensin converting enzyme inhibitors and calcium channel blockers) and non-steroidal anti-inflammatory drugs.

Like our study, the other study done in different other center, age of most of the patients with psoriasis with DM and/or HTN was also within the age group of 41-50 years. Distribution of study subjects according to blood pressure: mean ±SD of systolic blood pressure was found 130.08±18.42 mmHg and the diastolic blood pressure 82.67±7.04 mmHg in group A and it was 120±13.74 mmHg and 78.80±9.31 mmHg respectively in group B. Results were significant between the two groups (p<0.05).

Distribution of the study subjects on the basis of fasting plasma glucose (FPG) and 2 hours post prandial glucose (2 PPG). It was observed that FPG in group A and group B were 102±27.67 mg% and 92±15.37 mg% respectively which was highly significant. On considering the 2 PPG between the two groups it was found 144.75±49.98 mg% in group A and 127.20±27.27 mg% in group B which is statistically highly significant at p=0.05 level.

Over and above it was also observed that 43.3% of the randomly assigned study subjects in group A was found to have DM in comparison to only 16.7% of group B.
patients with having DM which was highly significant statistically. On the other hands when we consider the HTN, 38.3% of the patients in group A was found to have HTN in comparison to group B where there was only 13.3% of patients was with HTN which is highly significant at p=0.002 level.

Duration and severity of illness, BMI, age of the patients, family history of the diseases, drugs, smoking history and others associated cardiovascular risk factors may contribute in the genesis and development of DM and HTN in patients with psoriasis.

Through previous cross-sectional studies, investigators have demonstrated an association between several classic cardiovascular risk factors and psoriasis. HTN, DM, obesity, smoking and dyslipidemia have been found to be more prevalent in patients with psoriasis.5-11

A retrospective chart review of 753 psoriasis patients from an academic dermatology practice was performed in USA between 1997-2000, co-morbid diagnoses were listed in 551 out of 753 (73%) charts.12 In a case control study in Israel with over 46000 patients with psoriasis, investigators found the patients to be only at an increased risk of diabetes, but of artherosclerosis as well.13

The age adjusted proportion of DM among the study subjects was found significantly higher in psoriatic patients in compared to control group (odds ratio 1.38 p<0.05). This study supports previous reports of an association between psoriasis and DM (Cohen et al 2008). The risk of DM among individuals with psoriasis has been shown in different cross-sectional studies was found to be elevated, with a relative risk (RR) between 1.27 and 2.48, consistent with our study.14

In one COHORT study done in UK, of 3603 patients with severe psoriasis have established cardiovascular risk factors than patients without psoriasis.4 An increased risk of hypertension of 1.2 to 2-fold has been reported in cross-sectional studies. In our study, individuals with psoriasis were at a slightly increased risk for HTN in psoriatic patients than controls (43.3% versus 16.7%, or 3.824 and 38.3% versus 13.3% or 4.054. In our study, DM and HTN are found significantly more common in psoriatic patients in comparison to patients without psoriasis but having others skin diseases. This study was also consistent with the previous study.10

Some study found higher (up to 89%) family association with childhood psoriasis.14 But here among the psoriatic patients, family history of psoriasis was present among 30% of the patients.

The most common of which is chronic plaque psoriasis, affecting 80% to 90% of patients with psoriasis. The hallmark of classic plaque psoriasis was well-demarcated, symmetric and erythematous plaques with overlying silvery scale. Plaques are typically located on the scalp, trunk, buttocks and extremities but can occur anywhere on the body. Patients might demonstrate nail involvement, which can present without concomitant plaques.16 Active lesions might be itchy or painful. Where as in our study clinical findings in psoriasis patients scaling was present in all the cases followed by Auspitz sign, koebnerization, itching, scalp involvement and nail change.

DM and HTN in psoriatic patients need long term follow up and it is speculated that long duration is required for the development of DM and HTN in patients with psoriasis. As the present study period was short and within this short period, the association of DM and HTN with psoriasis could not be sought out and it is not wise to determine a conclusive and representative association among these three (DM, HTN and psoriasis) chronic co-morbid and long standing diseases. We suggested and recommended a long-term study with a more larger sample size to determine the actual prevalence of DM and HTN in psoriatic patients. Another COHORT study among psoriatic patients was required in Bangladesh to find out the actual prevalence of DM and HTN in psoriatic patients among the Bangladeshi population.

Limitations

This study was a single-center study with and small sample size. Long-term follow up had not done as the study duration was short. As the sampling technique was purposive and only patients admitted or visiting the CMCH were included in the present study, the result may not show the actual national scenario of our country.

CONCLUSION

In conclusion, our study indicates that, patients with psoriasis have an increased risk of DM and HTN, confirming the findings from previous several case control and cross sectional studies. Contribution of others cardiovascular risk factors could not be ruled out in the genesis of these systemic diseases.

These data illustrate the importance of considering psoriasis as a systemic disorder rather than simply a skin disease. Awareness of concurrent diseases will provide the clinician an opportunity to screen for others systemic diseases like DM and HTN.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Altobelli E, Patressilli R, Massareere M, Altemare G, Argenzia G, Giaretti A, et al. Risk factor of hypertension, diabetes and obesity in Italian psoriasis patients: a survey on socio-dermagraphic
characteristics, smoking habits and alcohol. 2009. Eur J Dermatol. 2009;19(3):252-6.
2. Amstrong AW, Lin SW, Chambers CI, Soklov ME, Chin DL. Psoriasis and hypertension severity: results from a case-control study. PLoS One. 2011;6(3):18227.
3. Binazzi M, Calandra P, Lisi P. Statistical association between psoriasis and diabetes: further results. Arch Derm Res. 1975;254(1):43-8.
4. Christophers E. Psoriasis-epidemiology and clinical spectrum. Clin Exp Dermatol. 2001;26(4):314-20.
5. David EE, Rosalie E, Bernet LJ, George FM. Lever’s Histopathology of Skin. 11th ed. Lippincott Williams and Wilkins; 2005.
6. Federman DG, Shelling M, Prodanovich S, Gunderson CG, Kirsner RS. Psoriasis: an opportunity to identify cardiovascular risk. Br J Dermatol. 2009;160(1):1-7.
7. Nicholus AB, Nicki RC, Brian RW. Davidsons’s Principles and Practice of Medicine. 23rd ed. Edinburg: Churchill Livingstone; 2018.
8. Gelfand JM, Shin DB, Neimann AL, Wang X, Margolis DJ, Troxel AB. The risk of lymphoma in patients with psoriasis. J Invest Dermatol. 2006;126(10):2194-201.
9. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. J Am Med Assoc. 2006;296(14):1735-41.
10. Fuxench ZCC, Shin DB, Gelfand JM. The risk of lymphoma in patients with psoriasis: A cohort study in the United Kingdom. J Invest Dermatol. 2016;136(5):S5.
11. Gibson SH, Perry HO. Diabetes and psoriasis. AMA Arch Derm. 1956;74(5):487-8.
12. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol. 2005;141(12):1527-34.
13. Hu G, Sarti C, Jousilahti P, Peltonen M, Qiao Q, Antikainen R, et al. The impact of history of hypertension and type 2 diabetes at baseline on the incidence of stroke and stroke mortality. Stroke. 2005;36(12):2538-43.
14. Huerta C, Rivero E, Rodríguez LAG. Incidence and risk factors for psoriasis in the general population. Arch Dermatol. 2007;143(12):1559-65.
15. Bhuiyan MSI, Zakaria ASM, Sultana A, Haque AKMZ, Shawkat SM. Clinico-epidemiological study of childhood psoriasis. Bangabandhu Sheikh Mujib Med Univ J. 2017;10(2):119.
16. Kim WB, Jerome D, Yeung J. Diagnosis and management of psoriasis. Can Fam Physician. 2017;63(4):278-85.

Cite this article as: Jamal S, Karim SA, Raihan SMR, Biswas R, Alam M. Diabetes and hypertension in patients with psoriasis: a cross sectional and case control study in a tertiary care hospital of Bangladesh. Int J Res Med Sci 2021;9:2217-24.