Psoriasis and Cardiovascular Risk Profile : A Comprehensive Review.

Abstract:

Psoriasis is an inflammatory immune-mediated ,chronic skin disease with a wide range of co-morbidities involving complex pathogenic interactions between the innate and adaptive immune systems.In psoriasis sufferers,there is increased probability of having other health conditions such as cardiovascular illnesess.A growing number of studies show that classic risk factors which leads to cardiovascular diseases and metabolic syndromes are common in psoriasis patients, leading to greater cardiovascular burden.The present article aims to synthesize what is known in the literature concerning the epidemiological and clinical data relating cardiovascular risk factors and psoriasis.The many pathophysiological mechanisms which justify this associations for stratification of the risk profile in psoriatic patients are also reviewed along with the implementation of different cardiovascular prevention strategies .The benefits and drawbacks of the numerous therapies which is frequent used in the prevention of cardiovascular diseases and analysis of specific psoriasis medications which have impact on risk factors of cardiovascular illnesses or the significant arterial events in the psoriasis patients.The detailed assessment of the various cardiovascular risk profiles in those patients who are suffering from psoriasis has been discussed profoundly.Also the several mechanisms involving the inflammatory cytokines released from the cells during inflammation specially in the dyslipidemia,atherogenic process resulting in plaque formation,hypertension, diabetes ,obesity and even the efficacy of statins has been reviewed from the sources of different articles published in different parts of the world.

Keywords: Psoriasis; immune mediated; chronic skin disease ; cerebral vascular events; cardiovascular diseases; cardiovascular risk ; inflammation; hypertension

Introduction :

Psoriasis is an inflammatory immune- mediated and chronic skin disease with several co-morbidities that includes the complex interactivities between both types of immune systems which is innate and adaptive immune systems of the body and affects about 2% of the population(1).

Psoriasis is a multisystemic inflammatory disease, which has its frequent association with various co-morbidities particularly, of severe events such as cerebrovascular diseases namely stroke and cardiovascular diseases(2,3).Evidence based studies which have been published in various parts of the world have shown that the frequency of risk factors involved in the development of cardiovascular events in the physical body namely ,smoking ,hypertension, obesity, physical inactivity hyperlipidemia ,diabetes mellitus and sub clinical atherosclerosis are elevated in psoriasis patients (3,4).The pivotal role of inflammation in the body along with

metabolic diseases have been shown to produce increased risk of cardiovasculare illnesses by their collaborative action in these patients(5).Also ,epidemiologic studies such as McDonald and et al showed that the hazards linked with all vascular events was 2.2 fold increased in the hospitalised psoriasis patients when comparison was done with the controls with other dermatological conditions (6).

The present review aims to synthesize the knowledge in literature about the epidemiological and clinical based corroboration which gives the connection between the various factors causing development of cardiovascular events and diseases to psoriasis.Also, the application of different cardiovascular prevention strategies such as aspirin, anti hypertensive therapy, lipid lowering drugs , hypoglycaemic agents are discussed for evaluating the response of specific medications of psoriasis on severe cardiovascular risk factors and diseases.

A detailed assessment of cardiovascular risk profiles in psoriasis patients :

- **Hypertension**

  Many studies have concluded that there is substantial associations between the prevalence of hypertension and psoriasis disease(7,8,9,10).Hypertension was found to be more common in those with mild psoriasis, with an odds ratio of 1.30 and similarly, a ratio of 1.49 for severe psoriasis, according to a meta analysis(11).Hypertensive patients have been shown to have elevated chances of developing psoriasis in a health study involving 77,728 nurses of hospitals (12). A recently conducted case control study suggested that those patients who have both psoriasis and hypertension were five-fold more on mono therapy anti- hypertensive regimen ,9.5 times increased chance of being on dual hypertensives and 16.5 times on triple anti hypertensive treatment than patients within psoriasis (8).

- **Diabetes mellitus**

  Various groups of studies conducted have shown that the frequency of diabetics is greater in psoriasis sufferers (7,8,9,10).In 108,132 patients who were suffering from psoriasis, the menace ratios for the incidence of diabetes mellitus type 2 were 1.11 in mild psoriasis and 1.46 in severe psoriasis group(13). Another recently published article including studies of eight cohorts has reported a relative risk of 1.50 for incidence of diabetes in psoriasis patients(14).A number of factors such as increase in obesity,decreased physical activity, unhealthy lifestyles has been shown to be linked to insulin resistance which is associated with inflammatory mechanisms.Many genetic pathways including incretin effect and genes such as CDKAL1, PTPN 22, ST6GAL1, JAZF1 are also involved and related to both diabetic patients (type 2)and psoriasis as well(15,16).

- **Dyslipidemia**

  According to many studies, a higher frequency of

dyslipidemia was suggested in psoriasis patients (7,8).Increased probability of cholesterolemia has been found to be linked with patients of psoriasis(1).Psoriasis is found to be associated with atherosclerosis and other lipid abnormalities discovered even during five years prior to the onset of psoriasis [17].Also, a recently published article showed that the average oxidised LDL concentration in patients of psoriasis were discovered to be greater than those of study controls [18].

Atherosclerosis is initiated by the accumulation of small LDL particles in tunica intima and by undergoing oxidation, producing oxidised LDL (oxLDL)which transforms into foam cells upon

entering macrophages and thereby,leading to atherosclerotic plaques formation.(19)The vascular wall cells are injured by all the products of oxidised LDL.Thereafter, the inflammatory cytokines and mediators promotes low grade inflammatory processes leading to further progression of the disease(19).Whereas HDL acts as a chemical shuttle for cholesterol transfer from peripheral tissues to the liver and also suppressing the various atherogenic mechanisms(19).Psoriasis patients were found to have significantly higher mean oxLDL in some studies. Mehta et al also enlightened the fact that the effluent capacity of high density lipoproteins which is mainly involved in the inhibition of atherogenic mechanisms by altering the cholesterol transport and monocytic infiltration, was significantly diminished beyond the factors which helps in the increased chances of developing cardiovascular diseases in psoriasis patients(20).The formation of atherosclerosis including higher hazard of cardiovascular illnesses is closely linked with the levels of apolipoprotein B , the main apoprotein component of LDL cholesterol. Lipoprotein (a) is another form of LDL which has apolipoprotein B bridged by disulfide bond to apolipoprotein-a and has both roles in atherogenicity and thrombus formation. Lipoprotein a is also very much susceptible to lipid peroxidation. A meta-analysis which was recently released has conveyed the theory that apolipoprotein B and lipoprotein a levels were discovered to be more common in psoriasis patients when compared to the controls of the study(21).

- **Obesity**

Several studies have published that psoriasis is coupled with the increased prevalence of obesity, particularly central obesity(7,18,19).An Argentinian prototype study (1286 psoriasis patients and 2547 controls) has obtained that the frequency of overweight ($p<0.01$ and 43% vs. 40%) and obesity ($p<0.01$, 30% vs. 24%) were significantly more in those who has psoriasis in comparison with the controls [22]. A study conducted in Denmark found out that many adolescents who have mild psoriasis were facing obesity (8.6% vs. 1.7%, $p = 0.008$), and the body measurements of abdominal obesity were also higher in comparison with the study controls (23).

- **Metabolic syndrome**

Metabolic syndrome consist of hyperglycaemia, central obesity, hypertension and dyslipidemia . It has been elicited that Metabolic abnormalities is linked with a twofold increment in having the consequences of cardiovascular events or diseases and a 1.5 times increment in death [24].A recently published meta-analysis article which included 63 studies encompassing a total of 15 ,939 patients with psoriasis and 103,984 study controls have observed that 30.3% of psoriasis patients were obtained with Metabolic syndrome in comparison with 21.7% subjects in the control group [25]. Also a meta-syntheses has revealed the linkage between psoriasis and metabolic syndrome which was found to be elevated South America [26]. Thus ,we come to the conclusion that the Interleukin -23 and Th17 cells can be an association between cutaneous and metabolic features in psoriasis patients [27].

- Addictions of cigarette smoking and alcohol use

Addictive habits for instances, smoking cigarettes ,bidis and alcohol consumption are already well-known risk factors which plays a role in the increased incidence of cardiovascular diseases .Various studies enlightened the incremental frequency of alcohol use and habits of cigarettes smoking in psoriasis sufferers (28,29,30).A published meta-syntheses showed the notability and substantial linkage between cigarette smoking and the graveness of psoriasis

illness.The role of nicotine in production of elevated levels of cytokine secretions namely, IL -12,2 (interleukin) in the pathogenesis of psoriasis have been found. Cigarette smoking produces free radical ions, interferes with MAPK pathways (mitogen-activated protein kinase), JAK-STAT pathways ,NF-kB(nuclear kappa B) pathways which are relevant to psoriasis. A crucial role played by nicotine in the origin of psoriasis by elevating the levels of secretion of cytokines namely,tumour necrosis factor (TNF), IL-12, and G-CSF also(31).This facilitates keratinocytes adhesive quality and migration in the skin and interfere with immune cell signaling , thereby causing immunomodulatory effect(32).

- **Physical activity**

A meta analysis which included a combined data of 13 studies with 149,499 participants reported that not much difference was obtained in the exercise done by the psoriasis patients and those without psoriasis when the total effect was analysed thoroughly(33). However another meta analysis showed that psoriasis sufferes did robust exercise significantly less when compared to the study groups with a relative risk of 0.76 and p less than 0.00001. Lower intensity exercises were more linked to psoriasis patients with more psoriatic lesions and self -awareness.A study conducted in the America in which the connection of physical activity and psoriasis was clearly evaluated, also showed that less hazard of psoriasis was independently associated with vigorous physical exercise(34).Physical activity can affect the risk of psoriasis through the role of systemic inflammatory mediators.

- **Cardiovascular prevention strategies**

Statins are the keystone in the management of cardiovascular risk .According to a recently published study,the appropriate candidates for statin therapy was analysed by assessing two strategies of cardiovascular prevention in psoriasis patients(35). A study encompassing atorvastatin with diabetes patients and secondary cardiovascular prevention statin trials were included in a post hoc analysis(36). It reported that total cholesterol ,LDL cholesterol ,similar apolipoprotein B were reduced in patients who has psoriasis and those not having psoriasis when given statins therapy. Many societies involved in atherosclerosis and Rheumatism in Europe and ESC also recommended to use a multiplying factor such as 1.5 for adjusting the calculated risk and following the statin therapy of the mass population while the other thinks of psoriasis as a chronic disease that increases the elevated chance of developing cardiovascular diseases,thus favouring the statins use in people who has intermediate risk (37,38). The results shows that only some should be given statin regimen. High intensity statins decreases the LDL cholesterol levels by more than 50%.A comprehensive randomised clinical study showed that severe psoriasis disease may have improvement by statin therapy (39).

Aspirin

NSAIDs has been found to be linked with increased exacerbations in psoriasis patients but another study has provided that there may be no link between the probability of having psoriasis or patients with joint problems manifesting as arthritis and use of aspirin (40).

- **Anti hypertensive therapy**

Beta blockers have been found to be associated with exacerbations of psoriasis.(41,42,43).Beta adrenergic receptors in skin is inhibited by beta blockers and leading to less intracellular levels of CAMP(cyclic adenosine monophosphate) which has a crucial role in differentiating and preventing cell proliferation. In T cells, the mechanisms of phosphorylation is elevated by them and it causes cellular hyperproliferation and psoriasiform change by surplus release of enzymes from neutrophils and macrophages and lymphocytes as well(44,45).Also, the increased hazard of having unchecked blood pressure was associated with severe form of psoriasis (46).

- **Hypoglycaemic agents**

Various evidences suggested that biguanides such as metformin therapy lowers the chances of having psoriasis in diabetics(47,48).Several hypoglycaemic drugs used in the therapy of diabetes mellitus (type2 mainly)such as glucagon-like peptide -1 receptor agonists,dipeptidyl peptides-4 inhibitors ,thiazolidinediones and biguanides ,has beneficial effects on psoriasis(49).The most frequently used anti diabetic drugs is Metformin which has been reported to lower the probability of psoriasis in diabetics(47,48).Also a randomised controlled trial elicited the patients of psoriasis with Metformin therapy having improved health when compared with the placebo drugs (50).

Imaging Techniques for Assessment:

For assessing sub clinical atherosclerosis and early atherosclerosis , indicators such as pulse wave velocity,carotid mid -intimal thickness ,endothelial function and coronary calcium score given by computed tomography are used in psoriasis patients particularly and autoimmune illnesses generally also(51,52,53,54,55).Carotid atherosclerotic plaques has been found in psoriasis patients and psoriasis patients with arthritis as well frequently(56,57).A frequent observation in severe psoriasis patients has shown a coronary calcium score of >400 even upon adjusting the risk estimates given by the Framingham score(58) .A recent meta study elicited that the psoriasis sufferers had higher probability of coro calcium score being greater than 0 and greater than 100 when compared with the study controls(59).

Approximation of the risk of developing increased cardiovascular diseases by using traditional scoring system has many drawbacks while these instruments of predictions were not specifically developed in psoriasis patients . However, the performance of these scores is suboptimal as the traditional cardiovascular risk factors do not fully explain the increased cardiovascular risk in patients with psoriasis, and current risk functions do not represent other contributing factors. Cardiovascular risk is often underestimated consequently as a result of the above factors(19) .Another meta analysis has shown that the Framingham scoring system has certain disadvantages when trying to correctly stratify psoriasis patients(60).Following a carotid ultrasonography examination,the majority of patients in the intermediate risk group and nearly half of those in the low-risk group were reclassified in a higher risk group . The underestimation of risk was showing increments in people who had psoriatic arthritis. A released article that has assessed the scores of risk factors gave a classification of the majority of psoriasis patients as “low risk” [61].

According to a study by Gisondi et al. also , the score of risk factors given by Framingham was very much increased in psoriasis patients than in comparison with the study controls at 5 years (mean $\pm$ SD 5.3 ± 4.4 vs. 3.4 ± 3.3, $p < 0.001$) and at 10 years (11.2 ± 8.1 vs. 7.3 ± 6.3, $p < 0.001$) [62].Also,a study proved that a reclasssification should be done after adding psoriasis as a factor in the scoring system such that the intermediate and high risk psoriasis should be given for the substantial percentage of patients having intermediate and low cardiovascular risk as given by the Framingham score (63). Few studies on various treatment modalities for psoriasis were reported(64-67).

Conclusions :

Several studies have shown that psoriasis is a multisystemic inflammatory autoimmune disease which has its impacts on not only skin and joints but also may be linked with cardiovascular co-morbidities .Higher frequency of risk factors which contributes notably in developing cardiovascular events or diseases such as hypertension, diabetes ,smoking ,obesity, dyslipidemia ,obesity ,metabolic syndrome has been shown to be associated with psoriasis

patients.The use of different cardiovascular prevention strategies and pharmacotherapy are being studied for better application of knowledge on psoriasis.Several article published in different parts of the world have shown that psoriasis is a multisystemic autoimmune disease with inflammation mechanisms which has its impacts on not only on bones, skin but also may be linked with cardiovascular co-morbidities .Higher frequency of risk factors which contributes notably in developing cardiovascular events or diseases such as hypertension, diabetes ,smoking ,obesity, dyslipidemia ,obesity ,metabolic syndrome has been shown to be associated with psoriasis patients.The use of different cardiovascular prevention strategies and pharmacotherapy are being studied for better application of knowledge on psoriasis.A growing number of studies show that classic risk factors which leads to cardiovascular diseases and metabolic syndromes are common in psoriasis patients, leading to greater cardiovascular burden.The present article aims to synthesize what is known in the literature concerning the epidemiological and clinical data relating cardiovascular risk factors and psoriasis.The many pathophysiological mechanisms which justify this associations for stratification of the risk profile in psoriatic patients are also reviewed along with the implementation of different cardiovascular prevention strategies .The benefits and drawbacks of the numerous therapies which is frequent used in the prevention of cardiovascular diseases and analysis of specific psoriasis medications which have impact on risk factors of cardiovascular illnesses or the significant arterial events in the psoriasis patients.The detailed assessment of the various cardiovascular risk profiles in those patients who are suffering from psoriasis has been discussed profoundly.Also the several mechanisms involving the inflammatory cytokines released from the cells during inflammation specially in the dyslipidemia,atherogenic process resulting in plaque formation,hypertension, diabetes ,obesity and even the efficacy of statins has been reviewed from the sources of different articles published in different parts of the world.

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