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Factors Influencing Insulin Biochemistry in UK Diabetic Patients

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Abstract:-
BACKGROUND: The growing prevalence and associated metabolic diseases of Diabetes Mellitus makes it a global public health concern. Empirical evidence demonstrates the influence of insulin biochemistry (metabolic parameters) – resistance, secretion, and sensitivity – in the development of Diabetes Mellitus; however, the factors underlying the biochemical behaviour these parameters and their associated impact level are noteworthy. Therefore, the aim of this review is to assess the factors influencing Insulin Biochemistry.
METHODS: Database-searched articles (using Advanced search with Boolean operators and the key search terms) and manually searched articles (Using Basic search and the key search terms), published between 1993 and 2013, that passed the predetermined inclusion/exclusion criteria were selected, critically appraised (using a CASP checklist), and the data analysed and synthesised using a narrative evidence synthesis. Microsoft office Excel application was used as the data extraction matrix for individual studies included.
RESULTS: 14 articles from 1074 database-identified articles were included for analysis, after the inclusion/exclusion criteria-based screening process. 11 of the studies focused on insulin resistance; while, the other 3 studies, focused on insulin sensitivity and insulin secretion. Physical, Dietary, Biochemical, Genetic, and Morbidity factors were significantly associated and correlated with insulin resistance; while, Exercise/Fitness and Medication/Supplementation factors were associated with insulin sensitivity and insulin secretion, across different population groups in UK.
CONCLUSION: Insulin parameters are influenced by both intrinsic and extrinsic biological factors; with the most predominant influence exerted by Biochemical, Genetic and Medication (Supplementation) factors.

Keywords:- *Insulin, Insulin Resistance, Insulin Sensitivity, Insulin Secretion, Diabetes Mellitus and United Kingdom.*

I. INTRODUCTION

Diabetes Mellitus (DM) is a growing public health concern is with an estimated at approximately 8.5%, globally; in the UK, a total estimated figure of about 2.9 million persons has been diagnosed with DM and over 850,000 undiagnosed (indicating a disease burden of 4.6%), it is estimated that 1 out of every 20 persons has DM whether diagnosed or not.[1, 2] DM is group of metabolic diseases known to be associated with high levels of blood sugar due to an alteration in the biochemistry of insulin typified by two main factors: the depletion of insulin in the blood as a result of the failure of the beta cells of the islets of Langerhans in the pancreas in secretion of enough insulin required for metabolic processes; and the decreased cellular insulin response, which depends on the resistance and sensitivity of various body cells to the produced insulin in circulation (Type II Diabetes.[3, 4]

Insulin resistance explains the opposition of body cells to the hormone, insulin; it is the most significant feature of pre-diabetes is insulin resistance, with T2DM as the commonest. Evidence suggests high heritable estimates for insulin resistance syndrome and beta cell function in families with high risk of T2DM.[5, 6, 7, 8]

Insulin secretion refers to the secretion of insulin hormone from the pancreas. Abnormalities in insulin secretion due to dysfunction beta-cells in the pancreas, as well as abnormalities in peripheral insulin action define the pathogenesis of the metabolic disease.[5, 6, 8] Insulin sensitivity is the responsive interaction of body cells with insulin.[5, 8] Biometric factors such as, age, sex, glycaemic control, and adipose tissue amounts role-play in the determination of insulin sensitivity in children and adolescent marked with T1DM.[9]

The review, thus, assessed the factors influencing Insulin Biochemistry (Metabolic Parameters) in UK diabetic patients (diagnosed and undiagnosed).

II. METHODOLOGY

2.1 Study Design and Protocol

The study design for this research is a Systematic review methodology and engages the following protocol: Framing Review question; Inclusion/ Exclusion criteria; Searching literature; Studies Selection and Data extraction; Quality appraisal of studies; Evidence Synthesis (Combining results and Data analysis); Results Interpretation; and Conclusions.[10]

2.2 Research (Review) Question

It is imperative, for an effective conducting of a systematic review that a clear, unequivocal, and well-focused and study-defined review (research) question be

constructed.[11] The review is: 'what are the factors influencing insulin biochemistry in UK diabetic patients (diagnosed and undiagnosed)?'

2.3Inclusion/Exclusion Criteria

The inclusion criteria include, Study must be primary research; Study must have been carried out in the UK; Study must have been published in English language; Study must examine Insulin Biochemistry (Insulin parameters) and the factors influencing them; and, Study must have been published in 1993 or later. The Exclusion criteria include, Study must not be primary research (Secondary study); Study must not have been carried out in the UK (Outside UK); Study must not have been published in English language (Non-English Language); Study must not examine Insulin Biochemistry (Insulin parameters) and the factors influencing them; and, Study must not have been published in 1993 or later (before 1993).

2.4 Search Strategy for Identifying Literature

The search strategy employed in this systematic review employed databases including, PubMed, MEDLINE, EBSCOhost (Discover), and CINAHL plus with full text. These databases were selected based on the reasons that are associated for their popularity among the professionals and experts for valid and peer reviewed journals and articles.[12]

Other databases searched were the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Effects (DARE).

2.5 Data Extraction

Data from all the included studies is extracted into electronic matrix of various headings and sub-headings, using a Microsoft Excel Spreadsheet program application. The matrix is grouped into various thematic headings, tailored to the review question, to minimise bias and improve the study's validity and reliability, as well as enhance data analysis and results.[13]

2.6 Quality Appraisal

This review employs a review-specific checklists from the Critical Appraisal Skills Programme (CASP) due to its structured questions relating to relevance, credibility, and rigour. Included studies are assessed, among other things to evaluate the impact of bias, as well as ascertain the degree of validity and reliability, to improve the trustworthiness of review.[11, 13]

2.7 ANALYSIS OF DATA

The analytical framework for analysing the data extracted from this research is narrative synthesis, given the non-homogeneity of information included studies have portrayed, and the characteristic features of the outcome measures, which make them statistically incomparable or not combinable.[14, 15]

2.8 Data Protection and Safe Keeping

Based on the requirements of the Data Protection Act, 1998, all the data extracted from the selected studies have been securely managed and access restricted to only researcher;[16] this is made possible through the password protection of the personal computer used all through the research, as well as safe keeping of all essential and sensitive materials with regards to this research and included studies.

2.9 Ethical Considerations

The study was approved by the Ethics committee, Institute for health Research (IHREC), University of Bedfordshire UK, (IHREC Application No.: IHREC252).

III. RESULTS

The findings from the studies discussing insulin resistance show that insulin resistance is determined by Physical, Dietary, Biochemical, Genetic and Morbidity factors. Studies relating to physical factors show that children from a South Asian ancestry are said to be more metabolically sensitive to adiposity; as such, prevention of T2DM is plausible through early prevention and/or treatment of obesity in children, namely south Asians; and that, insulin resistance in adult is determined by adult environmental factors, early childhood factors, intrauterine environment, as well as genetic factors. Further, evidence also shows that, there is an inverse association between the measures of lung function (FVC and FEV-1), which reveal volume of the lung, and insulin resistance and T2DM; and that these associations indicate childhood exposures, that influence lung growth as well as programme insulin resistance. While the study relating to dietary factor shows that DM is not common among non-milk drinkers; as such, individuals who do not drink milk are likely to be protected against insulin resistance as well as the metabolic syndrome.

Further, studies relating to biochemical factors reveal that there is an inverse association between adiponectin and factors strongly associated with DM development; as such, a strong DM risk marker. Also, that baseline serum (25[OH] D) is inversely associated with insulin resistance and future glycaemia, and associations form the basis for understanding the aetiology of metabolism of abnormal glucose; and that glucose intolerance in women is contributed by increase in adipose 11-beta-HSD1; and there is an association between 5-alpha reductase (A-ring reductase) and insulin resistance in both males and females. The protective and compensatory mechanism of preservation of insulin sensitivity could be provided by inactivation of augmented glucocorticoid.

Furthermore, studies relating to genetic factors show that TNF alpha (position -238) is associated with decrease in insulin resistance and may protect susceptible individuals from developing T2DM in the future. Also, a proportion of the total variance in insulin resistance as well as associated metabolic disturbances among Asian Indian families is significantly contributed by genetic factors; and that among the Asian groups (both in India and UK), predisposition to insulin resistance and its associated metabolic abnormalities seems to be rather genetically determined, and the impact of migration and environmental changes exerts only a small contributory effect. While the study relating to morbidity

factor shows that, insulin resistance seems to be a feature of hypertrophied heart, despite the absence of DM, hypertension, and coronary artery disease, which is partly rationalised, by the marked abnormalities in glucose transporters.

The study relating to exercise/fitness factor shows that high rates of fat oxidation due to continuous exercise training protocol induces the increased contribution of fat to substrate oxidation during the exercise and can lead to significant increase in insulin sensitivity, compared with a eucaloric interval training protocol. Whereas studies relating to medication and supplementation show that, following treatment with Pioglitazone, insulin sensitivity and Basal beta-cell function were improved, and that improvement in the ratio of Pro-insulin to insulin indicates that beta-cells are under reduced stress levels; and, that carbohydrate handling in the postprandial period is enhanced by prior acute high-dose resistant starch consumption, and this is attributed to the high rate of colonic fermentation.

Table 1 – Synopsis of Selected Studies

Authors/ Year	Title	Aim (Objectives)/ Hypothesis	Study Design	Target Population/ Sample Size	Findings and Outcome Measures
(Study 1) Lawlor, Smith and Ebrahim, (2003)	Life Course Influences on Insulin Resistance	To examine the independent associations of adult obesity and early life risk factors with insulin resistance.	Cross-sectional	British Women aged 60-79/ 1,394	Birth weight inversely associated with insulin resistance. WHR and BMI positively associated with insulin resistance.
(Study 2) Forouhi *et al*, (2008)	Baseline Serum 25 Hydroxy Vitamin D is Predictive of future Glycaemic Status and Insulin Resistance	To examine the association between the biomarker, serum 25-hydroxyvitamin D (25[OH] D), and markers of metabolic risk.	Prospective follow-up	Non-diabetic Nondiabetic Men and women/ 524 (214 men and 310 women)	Baseline 25[OH] D inversely associated insulin resistance and significant.
(Study 3) Tomlinson *et al*, (2008)	Impaired Glucose Tolerance and Insulin Resistance are associated with Increased Adipose 11 beta-Hydroxysteroid Dehydrogenase Type 1 Expression and Elevated Hepatic 5 alpha-Reductase Activity	Availability of decreased local glucocorticoid (through decreased 11-beta-HSD1 and/or increased A-ring reductase activity) will represent new physiological adaptive response to preserve insulin sensitivity.	Cross-sectional	Obese Patients (Men and Women)/ 101 (35 men and 66 women)	5-alpha reductase activity correlated with fasting insulin secretion and insulin resistance.
(Study 4) Lawlor *et al*, (2005)	Avoiding Milk is associated with a Reduced Risk of Insulin Resistance and Metabolic Syndrome	Assessing the association between milk consumption and insulin resistance as well as the metabolic syndrome.	Cross-sectional	British Women aged 60-79/ 4,024	Lower insulin resistance HOMA scores in non-milk drinkers compared to milk drinkers. Metabolic syndrome odds ratio of non-milk drinkers to milk drinkers = 0.55 (0.33, 0.94).
(Study 5) Lawlor, Ebrahim and Smith, (2004)	Associations of Measures of Lung Function with Insulin Resistance and Type 2 Diabetes	To examine the associations between lung function and insulin resistance, and T2DM.	Cross-sectional	British Women aged 60-79/ 3,911	FVC and FEV-1 inversely associated with prevalence of T2DM and insulin resistance. Adjusted odds ratios for DM prevalence were 0.80 and 0.85.
(Study 6) Wannamethee *et al*, (2005)	Association of Adiponectin with Metabolic and Vascular Risk Parameters in the British Regional	To assess the relationship existing between adiponectin and insulin resistance, inflammatory,	Cross-sectional	Non-diabetic men aged 60-79/ 3,640	Adiponectin significantly associated with insulin resistance.

	Heart Study Reveal Stronger Links to Insulin-related than to Coronary Heart Disease Risk-related Parameters	metabolic, and haemostatic risk factors as well as hepatic function.			
(Study 7) Zabaneh *et al,* (2009)	Heritability and Genetic Correlation of Insulin Resistance and Component Phenotypes in Asian Indian Families Using Multivariate Analysis	To assess the heritability and correlations in Asian Indian families.	Cross-sectional	Asian Indian men and women in the UK with Cardiovascular Heart Disease / 181	Insulin resistance has significant estimate of heritability. Genetic correlations between BMI and insulin resistance are statistically significant.
(Study 8) Nightingale *et al,* (2013)	Influence of Adiposity on Insulin resistance and Glycaemia Markers among UK Children of South Asian, Black African-Caribbean, and White European Origin	To assess the influence adiposity exerts on insulin resistance as well as glycaemia markers.	Cross-sectional	9- to 10-year-old Children in UK / 4,633	Positive associations between adiposity and insulin resistance.
(Study 9) Robertson *et al,* (2003)	Prior Short-term Consumption of Resistant Starch Enhances Postprandial Insulin Sensitivity in Healthy Subjects	To evaluate whether acute changes in the resistant starch (insoluble fibre) content would exert any effects on postprandial carbohydrate and lipid handling.	Cross-over Trial	Healthy men and women/ 10 (4 men and 6 women)	Higher levels of insulin sensitivity due to prior consumption of resistant starch.
(Study 10) Wallace, Levy and Matthews (2004)	An increase in Insulin Sensitivity and Basal Beta-cell Function in Diabetic treated with Pioglitazone in a Placebo-controlled Randomised Study	To examine the treatment effect of Pioglitazone on insulin sensitivity as well as the beta-cell function in T2DM.	RCT	30 subjects aged 35 – 47 with diet-treated DM	Insulin sensitivity increased by Pioglitazone. Increase in stimulated insulin sensitivity in group treated with Pioglitazone. Adiponectin and HOMA beta-cell function increased by Pioglitazone.
(Study 11) Paternostro, *et al,* (1999)	Insulin Resistance in Patients with Cardiac Hypertrophy	To examine whether myocardial insulin resistance is demonstrated in human cardiac hypertrophy, despite the absence of DM, hypertension, and coronary artery disease.	Cross-sectional	11 Normotensive non-diabetic patients and 11 control volunteers/ 22	During physiologic hyperinsulinemia, MGU reduced in patients.
(Study 12) Venables and Jeukendrup (2008)	Endurance Training and Obesity: Effect on Substrate Metabolism and Insulin Sensitivity	Hypothesise that continuous exercise training at an optimised intensity can result in greater measures of improvements in oxidation of fat and insulin sensitivity compared to a eucaloric interval	Cross-over Trial	Obese male/ 8	Increase in insulin sensitivity after the continuous training protocol.

		training program.			
(Study 13) Day *et al,* (1998)	Tumour Necrosis Factor-alpha Gene Promoter Polymorphism and Decreased Insulin Resistance	To assess the relationship existing between insulin resistance and two specific polymorphisms of the Tumour Necrosis Factor-alpha (TNF alpha) promoter region (positions -238 and -308).	Cross-over Trial	123 non-diabetic relatives of T2DM families and 126 control of no DM family history/ 249	Insulin resistance decreased in relatives marked with the TNF alpha allele – position -238.
(Study 14) Dhawan *et al,* (1994)	Insulin Resistance, High Prevalence of Diabetes and Cardiovascular Risk in Immigrant Asians, Genetic or Environmental Effect	To compare the prevalence of diabetes mellitus, hyperinsulinemia, as well as associated metabolic abnormalities.	Case Control	200 Men with Coronary Artery Disease and 191 control group/ 391	British and Indian Asians had higher WHR; and ratios positively correlated with the concentrations of insulin and triglyceride.

IV. DISCUSSION

Evidence from other previous studies shows that, Physical factors such as: weight, waist circumference, low birth weight, systolic blood pressure, exert a measure of regulatory effects on Insulin resistance.[17, 18] Correspondingly, studies included in this review evidences the influence of physical parametric factors including, BMI, WHP, as well as lung measures (FVC and FEV-1) on Insulin resistance, by their positive significant associations with Insulin resistance.[19, 20] Another included study demonstrated that adiposity is also positively associated with Insulin resistance, stating its sensitivity in children, especially South-Asians.[21] This suggests the influence of BMI, WHP, lung measures and, adiposity on Insulin resistance; thus, the plausibility of T2DM prevention through the prevention and treatment of DM risk factors such as obesity and childhood exposures – that programme Insulin resistance –, especially in children.

Dietary factors – carbohydrate beverage and Mediterranean diets –, as shown by previous studies, exert ameliorating effects on Insulin resistance;[22, 23] likewise, a study included in this review demonstrated lower HOMA Insulin resistance scores in non-milk drinkers compared to milk drinkers.[24] Thus, this implies that milk consumption in elderly women exerts an influence on Insulin resistance; as such individuals who do not drink milk are likely to be protected against Insulin resistance as well as the metabolic syndrome and DM.

Previous evidence shows a regulation of Insulin resistance by Biochemical components; serum iron overload, circulating triglycerides, hormones (serum leptin) are shown to be positively associated with Insulin resistance;[25, 26] while Insulin antibodies showed to exert ameliorating effects.[27] Similarly, three studies in this review reveal the influence of biochemical factors on Insulin resistance; stating an inverse association between adiponectin and serum (25[OH] D) with Insulin resistance and factors strongly associated with DM development non-diabetic men and women;[28, 29] as well as an association between 5-alpha reductase (A-ring reductase) and Insulin resistance.[30] These results evidences the influence of biochemical components on Insulin resistance and suggest that, Adiponectin (a fatty acid and glucose regulatory protein) is a strong DM risk marker; further, the associations between serum (25[OH] D) and Insulin resistance form the basis for understanding the aetiology of metabolism of abnormal glucose; while the association between 5-alpha reductase and Insulin resistance in both males and females suggest that, steroid metabolic activities role-play in the development of DM.

Three of the studies analysed evidence the influence of genetic related factors on Insulin resistance. The results reveal that TNF alpha (position -238) is associated with decrease in Insulin resistance in non-diabetic relatives;[31] also, Insulin resistance shows to have significant estimate of heritability, as well as statistically significant genetic correlations with BMI;[32] whereas higher WHR was reported among British and Indian Asians, and ratios are positively correlated with the concentrations of insulin and triglyceride.[33] These results, thus, suggest that susceptible individuals marked with TNF alpha allele (position -238), are likely to be protected from developing T2DM in the future. Further, given that, a proportion of the total variance in Insulin resistance as well as associated metabolic disturbances among Asians families is significantly contributed by genetic factors, predisposition to Insulin resistance and its associated metabolic abnormalities may be genetically determined, and the impact of migration and environmental changes exerts only a small contributory effect.

Insulin resistance is also evidenced to be influenced by a morbidity related factor. Another included study showed that myocardial glucose uptake (MGU) is reduced in patients with hypertrophied hearts in patients who are normo-tensive and non-diabetic; as well as a decrease in the ratio of insulin-dependent glucose transporters to insulin-independent glucose transporters.[34] This, therefore, implies

that Insulin resistance is seemingly a feature of hypertrophied heart, despite the absence of DM, hypertension, and coronary artery disease, which is partly because of the marked abnormalities in glucose transporters.

Results from studies analysed shows that exercise (fitness) and medication (supplementation) related factors exert a measure of influence on Insulin sensitivity; Insulin secretion is shown to be influenced by biochemical component and exercise (fitness) and medication (supplementation) factors.

Previous research evidence reveals that prolonged horseback-riding, resistive training, as well as habitual intensive physical activities exert a degree of on glucose metabolism, by improving insulin sensitivity.[35, 36, 37] Correspondingly, a study included in the analysis of this review evidences the influence of exercise (fitness) related factor on insulin sensitivity; reporting that a continuous exercise training protocol induces an increase in insulin sensitivity.[38] Thus, indicating that high rates of fat oxidation due to continuous exercise training protocol induces the increased contribution of fat to substrate oxidation during the exercise and can lead to significant increase in Insulin sensitivity.

Hyperbaric Oxygen treatment, vitamin D supplementation, as well as treatment with Rosiglitazone (an anti-diabetic drug), Low-dose of Growth hormone and Metformin exert regulatory effects on insulin sensitivity and insulin secretion – beta-cell function.[39, 40] This influence of medication (supplementation) related factors on insulin sensitivity insulin secretion is also evidenced in two studies included in the data analysis of this review; the result shows an increase in insulin sensitivity as well as an increase in stimulated insulin sensitivity in the treatment group that received Pioglitazone, anti-diabetic drug; the result also indicated an improvement in Basal beta-cell function. [41] Similarly, another included study reported higher levels of insulin sensitivity due to prior consumption of resistant starch.[42] This, therefore, suggests that anti-diabetic drugs exert a measure of influence on insulin metabolism, and the improvement in the ratio of Pro-Insulin to Insulin indicates that beta-cells are under reduced stress levels. Further, carbohydrate handling in the postprandial period is enhanced by prior acute high-dose resistant starch consumption, and this is attributed to the high rate of colonic fermentation, as such a DM protective mechanism.

The major limitation of the review is the estimation of the mechanism of effect of the various individual or group of factors influencing insulin biochemistry; for majority of the studies included, this remains quite unclear. As such, this leaves the review with little understanding about the biochemical processes involved during factors' influence on insulin biochemistry.

V. CONCLUSION

Insulin biochemistry (parameters) – insulin resistance, insulin sensitivity, insulin biochemistry –, are influenced by a range factor classified into: Physical, Dietary, Biochemical components, Genetic, Morbidity, Exercise (fitness) and Medication (Supplementation) factors; classified into Intrinsic and Extrinsic Biological factors, with regards to the source of factors' influence. Intrinsic biological factors include, Biochemical components, Physical, Genetic and Morbidity factors; while the extrinsic biological factors include Dietary, Exercise (fitness) and Medication (Supplementation) factors.

Further, the most (prevalent) predominant factors influencing insulin biochemistry (parameters) are Biochemical components, Genetic and Medication (Supplementation) factors; based on the analysis of data and previous evidence. While the impact of these factors is seen at two levels of effect: the regulation of the biochemical behaviours of the insulin metabolic parameters; and a secondary degree of impact that results to clinical dysfunctions and diseases as well as metabolic related syndromes.

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