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Original Research Article

Clinical Research Studies Involving Biomarkers in Obesity Registered in Clinical Trials Registry: An Audit

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Abstract

Background: The global obesity epidemic poses a significant public health challenge, increasing the risk of chronic diseases such as type 2 diabetes, coronary heart disease, and certain cancers, while also being linked to reduced life expectancy. The commonly used body mass index (BMI) is acknowledged as an imperfect measure of excessive body fat accumulation. Specific adipokines like leptin, adiponectin, and resistin are associated with obesity-related health outcomes, and ongoing biomarker research, employing high throughput methods, provides valuable insights into the etiology and pathophysiological pathways of obesity-related diseases.

This study focuses on analyzing clinical research and trials within the obese population, as documented in the public domain in form of clinical trials registry, emphasizing the necessity for high-quality data to better understand ongoing and completed trials and improve personalized prevention strategies for individuals at high risk of obesity-related diseases.

Aim and Objective: To analyse the research trials conducted in obese population with special reference to various biomarkers from data available on clinical trials registry website.

Material & Methods: This was a retrospective audit-based study. The official website of clinicaltrials.gov was assessed for data regarding different studies related to obesity and biomarkers from January 2007 to December 2023. The data was analyzed according to the multiple parameters. Data analysis and statistical analysis was done by using descriptive statistics in MS Excel.

Results: Primary outcome in majority studies was related to change in body weight/total fat mass which were mainly anti-obesity drug related trials. Around 22.81% studies belonged to Phase -1and Leptin (89.47%) followed by Adiponectin (47.37%) was the most studied biomarkers.

Conclusion: In conclusion, this audit sheds light on the fact that anti-obesity research is more market driven and fails to focus on the greater good of the society. It emphasizes the importance of generating high-quality data focusing on affordable and sustainable modalities of weight reduction and it effect on various biomarkers the elucidate the mechanism of adverse outcomes on cardiometabolic health aspects of the masses.

Keywords: Leptin, Adiponectin, Biomarkers

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Introduction

Obesity was declared a major public health problem and a global epidemic by the World Health Organization (WHO) in 1997. In general, a BMI of 25 kg/m2 or higher is considered overweight, and a BMI of 30 kg/m2 or higher is considered obese. [1] Worldwide, the prevalence of obesity has risen dramatically over the last four decades, and if current trends continue, the majority of the world's adult population will be overweight or obese by 2030. The prevalence in the United States was 41.9% from 2017 to March 2020 (2021 NHANES). Whereas the prevalence in India varies according to age, gender, geographical environment, socioeconomic status, and other factors. Obesity and central obesity prevalence rates range from 11.8% to 31.3% and 16.9% to 36.3%, respectively, according to the ICMR-INDIAB study 2015. [2] The problem of obesity is a major contributor to the global burden of chronic disease and disability, with serious social and psychological implications affecting people of all ages

and socioeconomic backgrounds. Obesity is a well-known risk factor for coronary heart disease (CHD), hypertension, stroke, ventricular dysfunction, congestive heart failure, cardiac arrhythmias, and type 2 diabetes, as well as certain cancers such as colorectal cancer, renal cell carcinoma, postmenopausal breast cancer, esophageal adenocarcinoma, pancreatic cancer, endometrial cancer, and liver cancer. [3,4]

BMI, which is presently employed to classify states of obesity, is only an imprecise indicator of body composition and could fail to adequately represent the risk associated with body fat distribution. [5] In nutritional science, there are four basic nutritional assessment methods, i.e., anthropometric, biochemical, clinical, and dietary methods, and obesity can be assessed through these methods. [6] Estimation of biomarkers which are the biological indicators for certain disorders is an objective and reliable method to assess obesity. Such biomarkers can provide compelling new insights into pathophysiologic pathways; potentially enhance clinical and public health identification of people at risk for disease; facilitate monitoring of disease progression and prognosis; serve as targets for interventions via diet, lifestyle, or drug treatment; and enable more personalized treatment decisions for individual patients. [4] As a result, the focus of this study is on analyzing clinical research and trials within the obese population as documented in the Clinical Trials Registry, emphasizing the importance of high-quality data to better comprehend ongoing and completed trials and improve personalized prevention strategies for individuals at high risk of obesity-related diseases.

Aim and Objective:

Aim:

To analyse the research trials conducted in obese population with special reference to various biomarkers from data available on clinical trials registry website.

Objective:

To analyse the research trials conducted globally in obese population according to the data available in the public domain from the clinical trials registry website with special reference to various biomarkers studied.

Materials and Methods:

Study Design and Study Population:

This is a cross-sectional observational registry – based "audit" of data available on the public domain of ClinicalTrials.gov website.

Inclusion criteria:

The research trials in which various biomarkers are studied in obese population will be included.

Study Procedure:

The study was initiated only after obtaining the approval from Institutional Ethics Committee, the official website was accessed and searched for studies with certain keywords like "obese", "biomarkers" "leptin" "cardiovascular risk". All search results of trials registered from 2007 to December 2023 were included in the study as per inclusion criteria. The data regarding the type of study, its primary outcome, biomarkers studied, etc was collected. Thus the "audit" of data available on the public domain of ClinicalTrails.gov website was carried out in this registry – based study. Data analysis was done using MS Excel.

Results:

A total of 57 studies conducted from the year 2007 to till date were included in the audit. On analysing the demographic parameters of study population in the various studies, it was observed that the female: male ratio varied across the studies with a female preponderance in participant recruitment. Different modalities studied in the clinical trials on obesity were - effect of drug (27 studies), effect of diet (20 studies), effect of exercise (5 studies), effect of diet+exercise (2 studies), etc.

Table 1 depicts that the clinical studies belonged to various phases of clinical trial. Maximum studies belonged to clinical phase 1 (13 studies) followed by phase 2 (12 studies) which suggests the primitive stage of drug development for obesity related treatment modalities. Also ,8-10 % of the studies belong to clinical trial phases 3 or 4 which suggest that as of today there are limited options for management of obesity despite of ongoing research and more molecular mechanisms/targets need to be explored, which can come from studying specific biomarkers. Therefore additionally, a lot of basic scientific research is ongoing in vitro on patient samples/sera to elucidate mechanisms and such 21 studies (36.84%) could not be classified under any of the clinical trial phases.

Table 1: Phases of Clinical trials related to Obesity and its biomarkers.

Study Phase	No. of studies (n=57)	Percentage
Phase 1	13	22.81
Phase 2	12	21.05
Phase 3	5	8.77
Phase 4	6	10.53
Not applicable	21	36.84

Various biomarkers related to obesity are being studied, and the most commonly used biomarker is Leptin (89.47%) followed by Adiponectin (47.37%) and Ghrelin (38.6%) . Biochemical parameters like blood glucose (47.37%) and lipid profile (47.37%) were also commonly studied as shown in Table 2.

Table 2: Biomarkers studied in various obesity related clinical trials globally.

Biomarker	No. of studies	% out of total
Leptin	51	89.47
Glucose	27	47.37
HDL	27	47.37
Adiponectin	27	47.37
Insulin	26	45.61
Triglycerides	26	45.61
Total Cholesterol	25	43.86
LDL	25	43.86
VLDL	22	38.6
Ghrelin	16	28.07
HBA1C	14	24.56
hs CRP	12	21.05
HOMA-IR	9	15.79
GLP1	8	14.04
TNF-α	8	14.04
IL-6	8	14.04
PYY	7	12.28
Free Fatty Acids	6	10.53
C Peptide	5	8.77
CCK	4	7.02
IGF-1	4	7.02
PAI-1	4	7.02
Neuropeptide Y	3	5.26
α- MSH	2	3.52
LPS	2	3.52
Glucagon	2	3.52
Orexin	1	1.75
Anti-leptin antibody	1	1.75
ESR	1	1.75
IL-1β	1	1.75
Triacylglycerol	1	1.75
Diacylglycerol	1	1.75

* α-MSH:α-Melanocyte Stimulating Hormone; CCK: Cholecystokinin; ESR: Erythrocyte sedimentation rate; GLP-1: Glucagon-Like Peptide-1; HBA1C: Haemoglobin A1c; HDL: High-Density Lipoprotein; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; hsCRP: high-sensitivity C-reactive protein; IGF-1: Insulin-like Growth Factor-1; IL-1β: Interleukin-1 β; IL-6: Interleukin-6; LDL: Low-Density Lipoprotein; LPS: Lipopolysaccharide; PAI-1: Plasminogen Activator Inhibitor-1; PYY: Peptide YY; TNF-α: Tumour Necrosis Factor-α; VLDLVery Low Density Lipoprotein.

On observing the primary objective of all the studies, it was noted that the most common primary outcome was related to either change in body weight or total fat mass.

Number of studies with Primary outcome related to change in body weight/total fat mass = 30
Pertaining to this observation, various permutations and combinations of obesity biomarkers studied in this group were noted as shown in Table 3.

Table 3: Combinations of biomarkers studied in obesity-related clinical trials globally.

Biomarkers studied	No. of studies	% out of total
Leptin + Adiponectin	27	90
Leptin + Adiponectin + Ghlerin	11	36.67
Leptin + Inflammatory markers	7	23.33
Adiponectin + Inflammatory markers	6	20
Adiponectin + Ghlerin	3	10
Leptin + Ghlerin	2	6.67
Leptin + Adiponectin + Ghlerin + GLP1	2	6.67
Adiponectin + PAI1	2	6.67
Leptin + PAI1	2	6.67

In majority of studies (26 studies) the average baseline BMI was clearly defined and ranged from 25 to >30 kg/m^2

Discussion:

The importance of biomarkers in obesity lies in their ability to serve as crucial diagnostic, prognostic, and therapeutic indicators, offering a deeper understanding of the underlying mechanisms and associated health risks. These biomarkers, including adipokines such as leptin and adiponectin, enable us to identify and monitor individuals at heightened risk of obesity-related diseases, such as type 2 diabetes and cardiovascular conditions. Additionally, biomarkers play a pivotal role in tailoring personalized interventions, facilitating targeted treatments, and enhancing preventive strategies. By providing measurable insights into the intricate physiology of obesity, biomarkers contribute significantly to the advancement of clinical research and the development of more effective approaches to tackle the global obesity epidemic.

The current audit reemphasised the fact of female preponderance which was put forth earlier by the authors of a community based survey done in south Asians and the study had also suggested a gender-sensitive population-level intervention to address cardiometabolic risk. [7] Majority of the trials and research focussed on anti-obesity drugs and dietary supplements which hold a big promising market that may hit the figure of 100 billion dollars according to the research cone by various economic experts like Goldman Sachs,Inc. Studies pertaining to calorie restriction ,exercise and life-style modification are limited and their relation to various biomarkers need to be more highlighted for overall sustainable models of societal wellbeing. Very limited authors from academia have reviewed the latter, but have failed to comment on the effect of such modalities on various biomarkers of obesity. [8]

Our study aimed at studying the various biomarkers of obesity that are being studied currently. A systematic review by Endalifer et. al mentions that the commonly and widely implemented biomarkers are microRNAs, inflammatory biomarkers, adipocytokines, oxidative stress, gut microbiotas, level of nutrients, and blood cell profiles. [9] Our study findings show that the most commonly studied biomarker was the adipocytokine-leptin whereas none of the studies has a mention of micro-RNAs.

As studied by Ouchi N et.al, Adiponectin has a protective role in obesity potentially by inhibiting tumor necrosis factor-alpha (TNF-α)–induced expression of cell adhesion molecules and inducing inhibitors of metalloproteinases via interleukin (IL)-10. [10,11] Out of the total 57 studies in this audit, 27 studies had adiponectin as one of the biomarkers investigated.

A study conducted by Aleksandrova K et. al. depicts that inflammatory biomarkers like C-reactive protein, interleukin-6, and tumor necrosis factor are commonly identified in the obese population. [12], as in obesity, in adipose tissues stimulates the release of inflammatory adipokines such as interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), monocyte chemoattractant protein-1 (MCP-1), and resistin are released owing to macronutrients' excess and finally leading to a state of chronic inflammation and increased adverse cardiovascular outcomes in these subjects. [13] But in our study, only 12 clinical studies had high sensitivity C-reactive protein while 8 clinical studies had IL-6 and TNF-α as the biomarkers studied. Lipid profile is commonly studied in association with obesity and related disorders as evident from our audit and other such studies. [14]

Musaad et. al conducted a study on biomarkers of obesity and further cardiovascular risks and Plasminogen Activator Inhibitor-1 (PAI-1) was found as an independent risk factor for obesity-related metabolic disorders. [15] Blood levels of PAI-1 correlate with body mass index and increased waist circumference and decrease following weight loss. [16]

Conclusion:

In conclusion, this audit sheds light on the intricate landscape of clinical research studies involving biomarkers in obesity. The anti-obesity research is more market driven and fails to focus on the greater good of the society. This audit is therefore an eyeopener and it emphasizes the importance of generating high-quality data focusing on affordable and sustainable modalities of weight reduction and it effect

on various biomarkers the elucidate the mechanism of adverse outcomes on cardiometabolic health aspects of the masses.

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