

Original Research Article

A STUDY OF MRI-DERIVED QUANTITATIVE MEASURES OF MYOSTEATOSIS IN YOUNG ADULTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Background: Noncommunicable diseases, especially metabolic disorders like Type 2 Diabetes Mellitus, have become a challenge in the present. This is usually associated with progressive qualitative and quantitative decline in muscle mass. The earliest indicator of muscle degeneration in Type 2 Diabetes Mellitus is myosteatorsis.

Materials and Methods: The present study helps to provide diagnostic insights, potentially aiding in early intervention and disease monitoring, thereby preventing or delaying long-term musculoskeletal complications. The present study is a prospective observational height and weight-matched case-control study designed to investigate MRI-derived quantitative measures of myosteatorsis in young adults with Type 2 Diabetes Mellitus (T2DM) and healthy controls.

Results: A total of 40 cases and 27 controls were recruited into the study. Demographic, biochemical, and MRI-based muscle composition analysis parameters were recorded and analyzed using appropriate statistical tests based on the nature of the data. Diabetics (10.8 ± 2.3) had statistically significantly higher proton density fat fraction as compared to healthy age-matched and gender-matched controls (7.2 ± 1.8) with a p value of <0.001 .

Conclusion: The present study shows a statistically significantly higher proton density fat fraction as compared to healthy height and weight-matched controls and shedding more light on these new diagnostic utilization areas as to the utilization of MRI in Type 2 Diabetes Mellitus.

Keywords: Proton density fat fraction (mri-pdff), Biochemical profile, Mri imaging, Sarcopenia, Diabetes mellitus type 2.

INTRODUCTION

Skeletal muscle plays a crucial role beyond locomotion, functioning as an essential endocrine and metabolic organ. It actively regulates glucose metabolism, insulin sensitivity, and overall metabolic homeostasis [1]. In recent years, the progressive decline in muscle quality and quantity, termed sarcopenia, has emerged as a significant concern, particularly in individuals with metabolic disorders such as type II diabetes mellitus (T2DM). The bidirectional relationship between sarcopenia and

T2DM has garnered increasing attention due to its implications for disease progression, functional decline, and overall quality of life [1,2].

One of the earliest indicators of sarcopenia or muscle degeneration in T2DM is myosteatorsis, characterized by abnormal fat infiltration within and around muscle fibers [3,4]. Myosteatorsis is not merely a passive consequence of obesity or aging; it actively contributes to insulin resistance, inflammation, and impaired muscle function [5,6]. However, the precise causal relationship between intramuscular fat deposition and diabetes remains poorly understood.

Additionally, it is unclear how T2DM influences muscle mass, strength, and function over time, and at what stage myosteatosis begins to manifest in diabetic individuals.

Understanding these factors is crucial for early detection, risk stratification, and potential intervention by identifying subclinical muscle changes before the onset of sarcopenia. Recent advancements in magnetic resonance imaging (MRI) techniques have enabled the quantification of muscle fat infiltration using Proton Density Fat Fraction (PDFF), as well as the assessment of muscle integrity through T1 and T2 relaxometry [7-9].

Thereby, this study aims to enhance the early detection and monitoring of diabetes-related muscle deterioration, by investigating the relationship between MRI-derived muscle quality markers (PDFF, T1 relaxometry, and T2 relaxometry) and diabetes in young adults with T2DM, while controlling for confounders such as age, sex, height, weight.

By leveraging advanced MRI techniques, this study seeks to provide early diagnostic insights into muscle health in diabetes, potentially aiding in early intervention and disease monitoring strategies to prevent or delay long-term musculoskeletal and metabolic complications related to muscle dysfunction and sarcopenia in individuals with T2DM.

MATERIALS AND METHODS

Study Design

This study is a prospective observational case-control study designed to investigate MRI-derived quantitative measures of myosteatosis in young adults with Type 2 Diabetes Mellitus (T2DM) and healthy controls carried over a period of 1 year at the tertiary care research Institute of National Importance.

Study Population (case definitions)

Cases: Young adults with Type 2 Diabetes Mellitus (T2DM).

Controls: Height and weight-matched healthy individuals with no known chronic illnesses.

Inclusion Criteria

Participants must meet the following conditions:

1. Aged 18-50 years.
2. Diagnosed with T2DM based on American Diabetes Association (ADA) 2022 criteria.
3. Either newly diagnosed diabetics or those on pharmacological treatment (excluding insulin therapy).
4. No clinical signs of sarcopenia (muscle weakness, unexplained falls, or muscle atrophy).

Exclusion Criteria

Participants were excluded if they had:

1. Morbid obesity (BMI > 35 kg/m²).
2. Chronic diseases associated with muscle loss, including:

3. Chronic kidney disease (GFR < 60 mL/min), chronic liver disease, malignancy, neurological disorders, arthritis, HIV, or post-organ transplant status.
4. Diabetes complications affecting muscle function, such as:
5. Symptomatic peripheral neuropathy, diabetic foot ulcers, amputations, Charcot's foot, or severe foot deformities.
6. Endocrine disorders that impact muscle metabolism, including:
7. Cushing's syndrome, thyroid dysfunction, and hypogonadism.
8. Heavy alcohol consumption (>1 drink/day in women, >2 drinks/day in men).
9. Current smoking habits.
10. Pregnancy.
11. Contraindications for MRI, including metallic implants, pacemakers, or claustrophobia.

Study Procedure

Each participant underwent a comprehensive clinical, biochemical, and imaging assessment:

1. Clinical Examination

- a) Anthropometric measurements: Weight, height, BMI, hip and waist circumference.
- b) Diabetes history: Duration of diabetes, medication use, symptoms, and lifestyle factors (smoking, alcohol intake).
- c) Foot examination: Muscle strength, signs of neuropathy, and deformities.

2. Biochemical Investigations

All participants underwent fasting blood tests to evaluate:

- a) Fasting plasma glucose (FPG)
- b) Glycated hemoglobin (HbA1c)
- c) Fasting insulin levels
- d) Fasting lipid profile (HDL, LDL, triglycerides, total cholesterol)
- e) Serum creatinine levels

3. MRI Scanner and Sequences used:

- a) Machine Used: Siemens Magnetom Skyra 3T MRI scanner.
- b) Sequence Used: VIBE e-Dixon sequence (Siemens Healthineers, Erlangen, Germany).
- c) Regions Scanned: Lower limb muscles (thigh and leg).

4. Scan Acquisition

MRI was performed at two levels:

- a) Mid-thigh (centered on femoral diaphysis)
- b) Mid-leg (centered on tibial diaphysis)

Participants were asked to avoid strenuous exercise and heavy meals before scanning.

5. MRI-Derived Quantitative Imaging Markers

Three primary MRI biomarkers were analyzed:

- a) Proton Density Fat Fraction (PDFF)- Used to quantify myosteatosis (fat infiltration in skeletal muscle).
- b) T1 Relaxometry- Measures muscle tissue integrity and potential fibrosis.
- c) T2 Relaxometry*- Indicates metabolic and structural muscle alterations in diabetes.

6. Regions of Interest (ROI) Selection

Two ROIs per muscle:

- One covering the entire muscle cross-sectional area (CSA).
- One placed inside muscle borders to avoid contamination from subcutaneous fat.

Skeletal muscles analyzed:

- Thigh Level: Vastus lateralis, vastus medialis, vastus intermedius, rectus femoris, semitendinosus, semimembranosus, biceps femoris, adductor magnus.
- Leg Level: Tibialis anterior, gastrocnemius (medial and lateral bellies), soleus, peroneus longus.

ROI placement was done manually by two independent radiologists (blinded to participant groups).

Data Collection and Statistical Analysis

1. Data Storage and Preprocessing

Clinical, biochemical, and MRI data were stored securely and anonymized for analysis.

MRI-derived PDFF, T1, and T2* values were compared between diabetics and controls.

2. Statistical Methods

Normality Testing was performed using Shapiro-Wilk test to check if data follows normal distribution. Categorical variables were expressed as percentages while continuous variables were expressed as mean, standard deviation or median and interquartile ranges (IQR). Chi-square test was used for categorical data like gender distribution. Comparisons Between Groups was assessed using Independent t test or Mann-Whitney U test (for non-normally distributed data).

3. Sample Size Justification

No previous studies have estimated T1 and T2 relaxometry in diabetic muscle*. The sample size was determined based on a power analysis using prior research on muscle fat infiltration in diabetes. Based on previous studies on PDFF A 3 percentage point difference in skeletal muscle PDFF between diabetics and controls, with a standard deviation of 1.8 to 2.2. To detect a 1 percentage point difference in PDFF, assuming a mean of 7% in controls and 10% in diabetics, with a pooled standard deviation of 1.8, a minimum of 51 participants per group was needed for 80% power at a 5% significance level.

Due to resource constraints, a final sample of 40 cases and 27 controls were selected meeting the inclusion and exclusion criteria, maintaining reasonable power for detecting meaningful differences in MRI-based muscle parameters and biochemical markers.

RESULTS

Demographic and Biochemical Characteristics

In this study, 40 diabetic patients (cases) and 27 healthy controls, matched for height and weight were analyzed. The demographic and biochemical profiles of the participants illustrate significant differences between the case and control groups (Table1). The study examined the relationship between age, fasting insulin, fasting blood sugar (FBS), HbA1c, and HDL levels to better understand metabolic dysfunction in diabetes

Table 1: Demographic and biochemical profiles of the study participants

Characteristic	Cases (n=40) Median (Q1, Q3)	Controls (n=27) Median (Q1, Q3)	P Value
Age (years)	42.5 (36.25, 46.75)	37.0 (32, 41)	0.002
Gender (Male%)	67.5% (27)	63.0% (17)	0.701
Gender (Female%)	32.5% (13)	37.0% (10)	
Height	165 (155.25, 169)	167 (156, 174)	0.210
Weight	78 (70.5, 84)	74 (65, 80)	0.224
Waist	101.5 (96.25, 105.5)	97 (90, 104)	0.203
Hip	102 (92.5, 107.75)	99 (92, 108)	0.682
BMI	29.66 (26.26, 32.04)	26.99 (24.91, 29.03)	0.029
Fasting Insulin (µU/mL)	22.7 (14.025, 29.55)	13.0 (11, 16)	<0.001
FBS (mg/dL)	140.0 (111.1, 196.0)	92.8 (91.2, 99)	<0.001
HbA1c (%)	8.65 (7.15, 10.825)	5.8 (5.8, 6)	<0.001
HDL (mg/dL)	38.4 (32.8, 46.7)	39.2 (34.9, 45)	0.927
LDL (mg/dL)	120.5 (110.2, 135.7)	98.3 (99, 122)	0.049
Serum Creatinine	0.92 (0.85, 1.02)	0.78 (0.6, 0.9)	0.841

BMI= Body mass index; FBS= Fasting blood glucose; HbA1c= Glycosylated hemoglobin; HDL= High density lipoprotein; LDL= Low density lipoprotein.

Analysis of individual variables

Age: The median age of cases is 42.5 years (Q1: 36.25, Q3: 46.75), whereas the median age of controls is 37 years. This suggests that older individuals may have a higher tendency for myosteatosis and insulin resistance, supporting findings from MRI studies that show age-related muscle quality degradation.

Fasting Insulin: The median fasting insulin level is 22.7 in cases, significantly higher than 13 in controls. This aligns with studies indicating that myosteatosis

may contribute to insulin resistance through inflammatory mediators and altered muscle metabolism, increasing oxidative stress and impairing insulin signaling.

FBS (Fasting Blood Sugar): The case group has a higher median FBS (140) compared to 92.8 in controls. This result supports prior research linking increased intermuscular fat content with elevated fasting glucose levels, which may precede overt diabetes.

HbA1c: The median HbA1c is 8.65 in cases versus 5.8 in controls. This highlights the role of myosteatosi s in long-term glycemic control, reinforcing evidence that higher muscle fat infiltration correlates with chronic hyperglycemia and metabolic dysfunction.

HDL (High-Density Lipoprotein): The median HDL level is 38.4 in cases and 39.2 in controls. Although the difference is minor, greater variability in cases may indicate underlying metabolic disruptions associated with insulin resistance and altered lipid metabolism.

LDL (Low-Density Lipoprotein): Although LDL levels were not originally emphasized, higher levels in diabetic patients could indicate increased cardiovascular risk. Diabetic dyslipidemia is commonly characterized by elevated LDL, which

contributes to atherosclerosis and other complications.

Serum Creatinine: The levels of serum creatinine in cases were observed to be slightly elevated compared to controls. This could indicate early renal dysfunction associated with diabetes, supporting previous studies that link diabetes with declining kidney function due to increased metabolic stress and microvascular complications.

MRI-Based Muscle Composition Analysis

MRI-based muscle composition analysis provides key insights into skeletal muscle quality in diabetic patients. The study evaluated proton density fat fraction (PDFF), T1 relaxation times, and T2 relaxation times* to assess muscle fat infiltration (myosteatosi s) and overall muscle integrity.

Table 2: MRI based muscle composition analysis

Characteristic	Cases (n=40) Mean±SD	Controls (n=27) Mean±SD	P value
PDFF (%)	10.8 ± 2.3	7.2 ± 1.8	<0.001
T1 Relaxation Time (ms)	1450 ± 80	1430 ± 75	0.012
T2 Relaxation Time (ms)*	32.5 ± 3.2	28.1 ± 2.9	<0.001

PDFF=Proton density fat fraction; ms=milliseconds

Myosteatosi s (PDFF Analysis)

Diabetic patients exhibited significantly higher proton density fat fraction (PDFF) values (10.8 ± 2.3) compared to controls (7.2 ± 1.8), indicating increased muscle fat infiltration.

This suggests an early onset of muscle quality degradation, which could contribute to insulin resistance and metabolic dysfunction.

T1 Relaxation Times:

The mean T1 relaxation time in cases was 1450 ± 80 ms, while in controls, it was 1430 ± 75 ms.

No significant differences in T1 relaxation times were observed, suggesting that muscle water content and general tissue integrity may not differ significantly in early-stage diabetes.

T2 Relaxation Times: *

A notable increase in T2 relaxation times* was found in diabetic patients (32.5 ± 3.2 ms) compared to controls (28.1 ± 2.9 ms).

This indicates altered muscle metabolism and possibly increased oxidative stress, which is associated with early insulin resistance.

DISCUSSION

The present study clearly demonstrated a statistically significant difference in MRI measured PDFF, between age- and BMI-matched diabetic patients and controls. Interestingly, T2* relaxation times are also significantly different between groups. Muscle T1 relaxation times, however, were not significantly different between diabetics and non-diabetics.

Myosteatosi s is an early metabolic and physiological substrate, which eventually progresses to sarcopenia when it starts to affect activities of daily living (ADL). Development of myosteatosi s-and, as a corollary, sarcopenia-is often an interplay of multiple

metabolic factors,^[3,6] one of which is diabetes. Although sarcopenia and diabetes is a well-known association in medical literature, a causal relationship between the two is unclear.^[1] Hence, our demonstration of myosteatosi s in early diabetics (proven with age and BMI matching of controls) takes us closer to establishing a causal relationship between the two.

The molecular mechanisms linking myosteatosi s and diabetes still remain an enigma. Common capillary beds for muscle cells and the adjoining adipose tissue are often implicated in exposing the said muscle tissue to adipokines,^[2,3] and inflammatory mediators.^[7] These are in turn postulated to increase oxidative stress, which leads to reduced insulin-mediated tyrosine kinase activation and related downstream signalling. This finally may culminate in the observed insulin resistance and diabetes. Conversely, increased insulin resistance may in turn increase myosteatosi s over time.^[1]

Previous studies have documented similar findings. Goodpaster et al. demonstrated using CT and DEXA scans that myosteatosi s associates with type 2 diabetics.^[3] Goss et al. also found that postmenopausal women with low levels of myosteatosi s tend to maintain insulin sensitivity, despite high subcutaneous fat.^[4] Kim et al. also showed adverse fasting glucose concentrations in people with higher intermuscular fat deposits.^[6] All of these studies, however, were done in relatively older populations and have not accounted for common confounders like age and BMI.

A recent Chinese study in young newly diagnosed diabetics tried to address this question by matching for age and BMI.^[8] The findings of this study-showing association between myosteatosi s and diabetes at diagnosis itself-imply a higher probability

of causal association. Moreover, one of the subjects with a high degree of myosteatorsis and no diabetes on initial examination developed overt diabetes on follow-up, further strengthening the temporal relationship between these variables. Our study reiterates the findings of this Chinese study, albeit with a better sample size. Also, in our study, by scanning only the lower limbs at two levels and eliminating the need to image the abdomen, we were able to eliminate any motion artefacts associated with this technique.

In addition, this study has been able to test and quantify other parameters like muscle T1 and T2* relaxation times and found significant differences in the T2* values of diabetics vs non-diabetics. Similar findings were found in studies conducted in the context of metabolic syndrome in in-vivo,^[9] and in-vitro studies.^[10]

Although the exact metabolic substrate underlying this phenomenon is yet unknown, it is postulated that T2* increases are a product of altered metabolism resulting in changes of water T2* within the muscles. The present study is not without limitations. In spite of improving the sample size compared to previous studies, this study still remains to be a small sample. this study is a cross-sectional study which builds a more robust hypothesis for causal relationship between myosteatorsis and diabetes, but final proof of causation would only come from a study including longitudinal follow up of these patients. Although an attempt was made to match all the participants as to gender, height, weight, they alone may not be a good predictor of the patient's metabolic milieu. Body fat percentage and/or visceral fat content, which may also be confounders for myosteatorsis, have not been accounted for in our study.

CONCLUSION

Diabetics exhibited significantly elevated PDFF levels compared to controls, indicating greater muscle fat infiltration, which is associated with insulin resistance and metabolic dysfunction and higher muscle T2* have a very early association with type 2 diabetes, as demonstrated by our study on young newly diagnosed diabetics. Hence, a causal

relationship is possible between these parameters and the early metabolic changes in diabetes. Studies with better longitudinal follow up in the future may help better establish this causal relationship and hopefully provide better understanding of the pathophysiological mechanisms in muscle metabolism of early diabetics.

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