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専　攻　名	医学専攻
学位論文題名	Effect of Pemafibrate on Hemorheology in Patients with Hypertriglyceridemia and Aggravated Blood　Fluidity Associated with Type 2 Diabetes or Metabolic Syndrome (2 型糖尿病またはメタボリックシンドロームで高中性脂肪血症の患者におけるペマフィブラートの微小血管における血液流動性に与える影響の検討)
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学位論文内容の要旨

1. Introduction

Persistently high serum triglyceride (TG) and free fatty acid (FFA) levels, which are common in type 2 diabetes and metabolic syndrome, are residual risk factors after significant low-density lipoprotein cholesterol (LDL-C) reduction by statin therapy for atherosclerotic coronary vascular disease. However, no definitive data show that reducing TG reduces cardiovascular events, and the impact of TG- and FFA-lowering therapy on microcirculation is still unknown.

To test our hypothesis that significant improvements in TG, remnant like particles cholesterol (RLP-C), and FFA levels by pemafibrate treatment normalizes hemorheology, we evaluate the effects of pemafibrate treatment on hemorheology and FFA levels.

2. Materials and Methods

2.1. *Patients*

The Ethics Committee of the Dokkyo Medical University Nikko Medical Center approved the study protocol. (Nikko 31016, 31017). The study design was a single-center, non-randomized, controlled study. The inclusion criteria were as follows: 1) age ≥ 20 years; 2) type 2 diabetes mellitus (HbA1c 6–10%) or metabolic syndrome [20], comorbid with fasting serum TG ≥ 150 mg/dL; and 3) whole blood transit time (corrected) > 45 sec on microarray channel flow analyzer (MCFAN).

Patients were divided into a study group, receiving pemafibrate 0.2 mg／day (n = 50) for 16 weeks, and a non-pemafibrate control group (n = 46). Blood samples were drawn 8 and 16 weeks after study entry to evaluate whole blood transit time as a hemorheological parameter, leukocyte activity by MCFAN, and FFA levels. The exclusion criteria were as follows: 1) patient treated by pemafibrate, fibrates, or omega-3 fatty acids; 2) patients deemed by the principal investigator or sub-investigator to be inappropriate for participation in the study. Finally, 96 patients were enrolled from May 2020 until December 2021, and 50 patients were newly prescribed pemafibrate 0.2 mg/day, and 46 patients were not prescribed pemafibrate according to the attending physicians' decision. All participants provided written informed consent.

2.2. *Statistical Analysis*

Baseline comparisons were conducted using the Wilcoxon rank sum test, Student's t-test, chi-squared test, and Fisher's exact test. Comparisons of the time-response curves of various parameters of the two groups were made by two-way repeated measures analysis of variance. The target number of patients was 41 for each group, totaling 82 ($\alpha = 0.05$, $1-\beta = 0.80$). We set the dropout rate for this study at 10%, and the required sample size was therefore 92 patients.

3. Results

All patients had similar baseline characteristics. No significant differences in the glycemic parameters between the groups were observed. The pemafibrate group showed a slight decrease from the baseline HbA1c level at week 16, although this was not statistically significant when compared with the non-pemafibrate group. Fasting serum TG levels of the non-pemafibrate group decreased from baseline 245.8 ± 112.6 mg/dL to 205 ± 139.6 mg/dL at week 8, and 220.5 ± 148.6 mg/dL at week 16. The pemafibrate group fasting serum TG levels decreased from baseline 278.6 ± 122.2 mg/dL to 161.8±101.1 mg/dL at week 8, and 135.5±49.1 mg/dL at week 16. RLP-C levels in the pemafibrate group decreased significantly from baseline 13.2 ± 8.7 mg/dL to 5.5 ± 3.1mg/dL at week 8, and 4.9 ± 2.5 mg/dL at week 16. Total cholesterol, LDL-C, HDL-C, and FFA levels remained unchanged in both groups. No serious adverse events were observed in either of the groups.

A two-way repeated analysis of variance showed no difference between the two groups in the effect of reduced TG concentration on blood rheology in the Ex Vivo microvascular model.

There was no difference in overall FFA values between the two groups. Subgroup analysis of FFA values above the median at baseline showed no significant interaction, but one-way analysis of variance revealed significant suppression of FFA values at

week 16 in the pemafibrate group compared to baseline ($p < 0.05$).

4. Discussion

We hypothesized that reducing excessive FFA levels with pemafibrate would prevent endothelial dysfunction and normalize blood rheology. However, our results showed no clear significant effects of pemafibrate on hemorheological data in patients with concurrent elevated TG levels and Type 2 diabetes or metabolic syndrome. The lack of benefit from pemafibrate was thought to be due to the small percentage of patients with high FFA. A possible reason for this is that we did not add FFA values to the entry criteria, as FFA values are not routinely measured in our clinical practice and were difficult to use for screening. It has been suggested that pemafibrate may indirectly stabilize the dynamic equilibrium of fatty acids by converting many TRL residues to LDL-C thereby lowering elevated FFA levels to the normal range. Abdominal obesity, as seen in hypertriglyceridemia and metabolic syndrome, increases total body fat and releases large amounts of fatty acids owing to increased adipocyte mass.

However, although obesity worsens the general health status, excess fat does not necessarily cause metabolic abnormalities, and the loss of the dynamic equilibrium between fatty acid release and consumption and the increase in FFA levels are thought to be responsible for endothelial dysfunction within blood vessels.

The study was a single-center, nonrandomized controlled trial with a limited sample size. Only 30% of the study population had elevated baseline FFA levels; therefore, additional studies are needed for patients with elevated FFA and TG levels and type 2 diabetes mellitus.

5. Conclusions

Although pemafibrate treatment decreased serum levels of TG, and RLP-C, it did not significantly improve blood rheology as reflected by whole blood transit time and leukocyte activity in patients with type 2 diabetes mellitus or metabolic syndrome complicated by hypertriglyceridemia.

論文審査結果の要旨

令和５年７月５日に福利厚生棟２多目的会議室での学位論文公開発表会において、本学位論文について審査が行われた。

「学位論文研究テーマの学術的意義」

２型糖尿病やメタボリックシンドロームによくみられる血清トリグリセリド（TG）および遊離脂肪酸（FFA）

の持続的高値は、動脈硬化性冠血管疾患に対するスタチン治療により低比重リポ蛋白コレステロール（LDL-C）を大幅に低下させた後も残存する危険因子とされている。しかし、TG の低下が心血管イベントを抑制するという決定的なデータはなく、TG および FFA の低下療法が微小循環に及ぼす影響もまだ不明である。ペマフィブラート治療のヘモレオロジーおよび FFA 値への影響を評価した。

1）年齢 20 歳以上、2）2 型糖尿病（HbA1c 6-10%）またはメタボリックシンドローム、空腹時血清 TG 150 mg/dL 以上を合併、3）マイクロアレイチャネルフローアナライザー（MCFAN）での全血通過時間（補正）＞45 秒。患者は、ペマフィブラート 0.2 mg/日を 16 週間投与する試験群（n = 50）と、ペマフィブラートを投与しない対照群（n = 46）に分けられた。試験開始 8 週後および 16 週後に採血を行い、血液学的パラメーターである全血通過時間、MCFAN による白血球活性、および FFA 値を評価した。

全患者のベースライン特性はほぼ同じであった。血糖値パラメーターに群間で有意差は認められなかった。ペマフィブラート群は 16 週目にベースラインの HbA1c 値からわずかに低下したが、非ペマフィブラート群と比較すると統計的に有意な差はなかった。総コレステロール、LDL-C、HDL-C、FFA 値は両群とも横ばいであった。また、両群とも重篤な有害事象は認められなかった。Ex Vivo 微小血管モデルにおける TG 濃度低下が血液レオロジーに及ぼす影響は二元配置反復分散分析により、両群間に差はなかった。ペマフィブラートの生体内抗酸化能と酸化ストレスへの影響 においてはペマフィブラートの投与開始により、非ペマフィブラート群と比較して BAP が時間依存的に有意に改善された。しかし、d-ROMs テストを用いて測定した血清中のヒドロペルオキシド濃度は、いずれの群でも有意な変化は認められなかった。

「学位論文及び研究の争点，問題点，疑問点，新しい視点」

1. 研究の設計や解析方法に関しては少し問題があるように思われる。
2. MCFAN による白血球活性の解析方法は臨床的に確立されるとは言い難い。