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Study of oral anti-diabetic therapy and effectiveness of such therapy on patients with type II Diabetes Mellitus of more than five years on treatment

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Abstract

Diabetes Mellitus will eventually cause cardiac, vascular, renal, hematological, ocular, and neuronal complications and will result in end organ failure. FBS, PPBS and HbA_{1c} are now the most important parameters for diagnosis and management of diabetes. In this study 150 patients with Diabetes Mellitus type II were enrolled from OPD's of Medicine and Surgery departments, MIMS. After fulfilling the selection criteria, patients were categorized into four groups according to the treatment schedule. Group –1 were on tablet Metformin (500 -1000mg), group – 2 were on tablet Glimepiride (1-4mg) group -3 were on combination of Metformin(500/1000mg) + Glimepiride (1-4mg) and group-4 with combination of Metformin (500/1000mg) + Glimepiride (1-4mg) + Pioglitazone (15-30mg). The efficacy variables taken in this study were percentage decrease in FBS, PPBS and HbA_{1c}. There is no significant difference between group-1(Metformin) and group-2 (Glimepiride) in lowering FBS, PPBS and HbA_{1c}. Metformin + Glimepiride and Metformin + Glimepiride + Pioglitazone, reduces the FBS, PPBS and HbA_{1c} levels more when compared to the Metformin/Glimepiride. Most of the drugs fail to achieve the glycemic control. This emphasizes the fact that patient education and compliance of therapy is urgently needed to prevent or reduce the risk of developing the complications.

Keywords: Diabetes Mellitus, Glimepiride, Metformin, Pioglitazone and Glycated Hemoglobin (HbA_{1c})

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Introduction

Diabetes Mellitus is characterized by hyperglycemia, altered metabolism of lipids, carbohydrates & proteins; and an increased risk of complications from vascular diseases.[1] Diabetes Mellitus will eventually cause cardiac, vascular, renal, hematological, ocular, and neuronal complications and will result in end organ failure. FBS, PPBS and HbA_{1c} are now the most important parameters for diagnosis and management of diabetes. The standard therapy available for Diabetes Mellitus is insulin and oral hypoglycemic drugs [2]. As on 2013, 382 million people have diabetes worldwide. Type II makes up about 90% of the cases [3]. This is equal to 8.3% of the adult population with equal rates in both women and men [4].

In 2012 it resulted in 1.5 million deaths worldwide making it the 8th leading cause of death.[4] More than 80% of diabetic deaths occurring in low and middle-income countries. [5] The greatest increase in rates was expected to occur in Asia and Africa, where most people with diabetes will probably live in 2030.[6] The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, including a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present.[6] In view to fulfill the objective of finding the most

effective therapy for type II diabetes mellitus in present population, the study is conducted first to assess the standing situation of current therapy practiced at this place [7].

Materials and Methods

In our study 150 patients with Diabetes Mellitus type II were enrolled from OPD's of Medicine and Surgery departments, MIMS. The study was conducted for a period of 18 months during the period of December 2012 to June 2014, on patients suffering from Type II Diabetes Mellitus attending the Medical and Surgical OPD's of Maharajah's Institute of Medical Sciences (MIMS) Hospital, Nellimarla, Vizianagaram district, Andhra Pradesh. The approval of Ethics committee (IEC) of MIMS was taken before the start of the study.

Study population: Total 150 patients who were already on treatment for type II Diabetes Mellitus for more than 5 years were enrolled in our study. Patients were categorized into four groups according to the treatment schedule. Group –1 were on tablet Metformin (500 -1000mg) ,Group – 2 were on tablet Glimepiride (1-4mg) Group -3 were on combination of Metformin (500/1000mg) + Glimepiride (1-4mg) and Group-4 with combination of Metformin (500/1000mg) + Glimepiride (1-4mg) + Pioglitazone (15-30mg). Including the both male and female with type II diabetes mellitus patients who were already on treatment for more than 5 years, Patients between the age group of 18 - 70 years were included in the study. Excluded those are Patients with type 1 diabetes mellitus, patients with severe debilitating diseases like renal failure and cardiovascular diseases, Patients with recent infections or major surgery. Patients with recent myocardial infarction (MI) and pregnant women were excluded from the study.

In this Observational study 150 patients with diabetes mellitus type II were enrolled from OPD's of Medicine and Surgery departments, MIMS. After fulfilling the selection criteria, patients were categorized into four groups according to the treatment schedule. Group – 1 were on tablet Metformin 500mg to 1000mg (n=38; 25.33%), Group – 2 were on tablet Glimepiride 1mg to 4mg (n=24; 16%). Group -3 were on combination of Metformin (500/1000mg) + Glimepiride (1-4mg) (n=58; 38.67%) and group-4 with combination of Metformin (500/1000mg) + Glimepiride (1-4mg) + Pioglitazone (15-30mg) (n=30; 20%). After obtaining informed consent, Standard laboratory procedures followed for the estimation of fasting blood sugar (FBS), and post prandial blood sugar (PPBS) by Glucose oxidase peroxidase method (GOD - POD Method) and glycosylated hemoglobin (HbA_{1c}) by Chromatography based HPLC assay.

Statistical Analysis: Using SPSS software version-16 statistical analyses was done. The treatment groups were compared for efficacy using Student's paired 't' test. All the obtained results were tabulated and compared using Student "t" test and graphical representation was done accordingly.

Results

The present study was conducted in the Department of Pharmacology, Maharajah's Institute of Medical Sciences (MIMS), Nellimarla, Vizianagaram during the period of December 2012 to June 2014 for 18 months. 150 patients of Type II Diabetes Mellitus ranging from 18 to 70 years age group were considered as subjects for the study. At the end of the study the following observations and results were obtained.

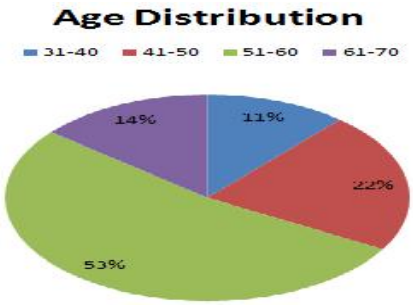

Figure 1: Age Distribution among the study groups

No patients were found from 18-30 years. No patient reported below the age of 31 years. The mean age 53.44 ± 9 years with a spread from 31-70years. The greatest number of patients were in the age group of 51-60 years [79(52.66%)] followed by 41-50 years [33(22%)], 61-70 years [21(14%)], 31-40 years [17(11.33%)].

FBS	Post R/values of Groups	N	Mean	SD	P value
Group 1 Vs Group 2	**Group 1**	**38**	**134.92**	**9.45**	**<0.218**
	Group 2	**24**	**131.96**	**8.63**	
Group 1 Vs Group 3	**Group 1**	**38**	**134.92**	**9.45**	**<0.0001**
	Group 3	**58**	**119.79**	**20.30**	
Group 1 Vs Group 4	**Group 1**	**38**	**134.92**	**9.45**	**<0.0001**
	Group 4	**30**	**105.37**	**19.77**	
Group 2 VsGroup 3	**Group 2**	**24**	**131.96**	**8.63**	**<0.0001**
	Group 3	**58**	**119.79**	**20.30**	
Group 2 VsGroup 4	**Group 2**	**24**	**131.96**	**8.63**	**<0.0001**
	Group 4	**30**	**105.37**	**19.77**	
Group 3 Vs Group 4	**Group 3**	**58**	**119.79**	**20.30**	**<0.0001**
	Group 4	**30**	**105.37**	**19.77**	

Table 1: Shows Variables of the post treatment values of FBS of all four groups

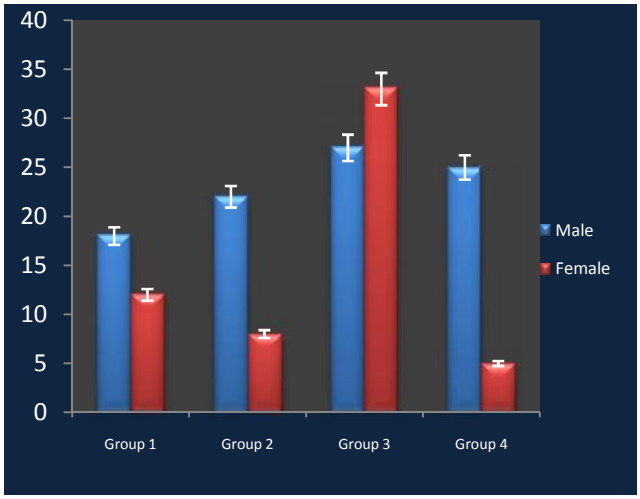

Figure 2: Sex Distribution among the study groups

Out of 150 Patients 92 (61.33%) were males and 58 (38.66%) were females. Predominantly males were suffering from the disease. Of this 92 male patients majority patients i.e, 36 (62.06%) were on group-3 therapy, 23(60.52%) were on group-1 therapy 20 persons (83.3%) were on group-2 therapy and 13 persons (43.3%) were on group-4 therapy. Out of 58 female patients- Majority patients i.e, 22 persons (37.93%) were on group -3 therapy, 17persons (56.6%) were on group-4 therapy, 15 persons (39.48%) were on group-1 therapy and least number of patients i.e four were on group-2 therapy.

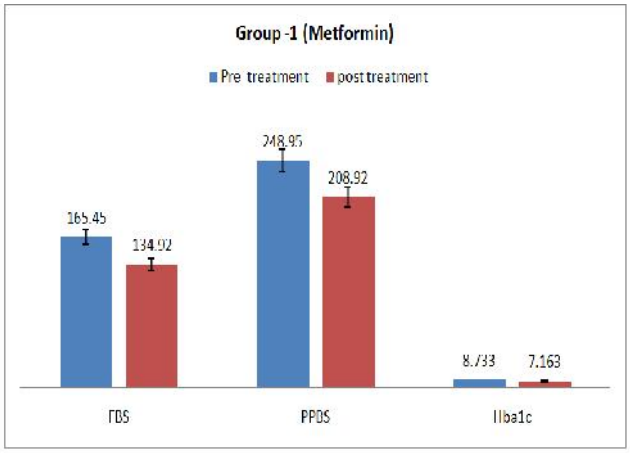

Figure 3: Characteristics of variables before and after administration of metformin (group-1) drug therapy (with in the same group).

There was a significant decrease in the mean value of FBS (Pretreatment = 165.45 mg/dl; Post treatment = 134.92mg/dl; p <0.0001,% of fall 18.31%); a significant decrease in the mean value of PPBS (Pre treatment= 248mg/dl; vs Post treatment = 207.97mg/dl; p < 0.0001,% and a fall of 16.14%); value of HbA_{1c} (Pre treatment = 8.7; Post treatment =7.163; p <0.0001, % of fall 1.19%) showed a similar response. Using the frequency intervals and frequency of range, bar diagram was prepared for the mean values of pretreatment and post treatment with in group – 1(Metformin).

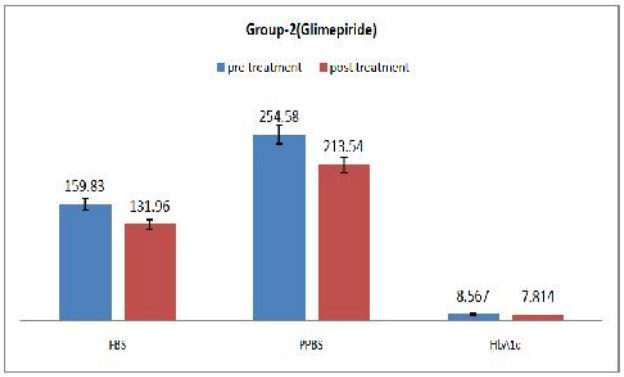

Figure 4: Characteristics of variables before and after administration of Glimepiride (group-2) therapy (within the same group).

Figure –4 shows the post treatment values of Glimepiride (1-4mg) compared with the pre treatment values. There was a significant decrease in the mean value of FBS (Pretreatment =160.3mg/dl; Post treatment= 131.96mg/dl; $p < 0.0001$,% fall of 17.84%); there was a significant decrease in the mean value of PPBS (Pretreatment= 254.58mg/dl; Post treatment = 213.54mg/dl; $p < 0.0001$,% fall of 15.12%); there was a significant decrease in the mean value of HbA_{1c} (Pre treatment =8.567; Post treatment =7.814; $p < 0.01$ with a fall of 1.0%).Using the frequency intervals and frequency of range, bar diagram was prepared for the mean values of pre treatment and post treatment with in group – 2 (Glimepiride).

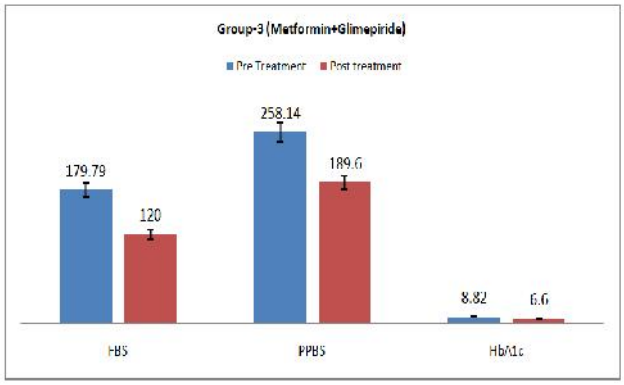

Figure 5: Shows the post treatment values of Metformin (500/1000mg) + Glimepiride (1-4mg).

Results of dependable variables before and after administration of Metformin + Glimepiride (group-3) drug therapy (within the same group) compared to the pre treatment values. There was a significant decrease in the mean value of FBS(Pre treatment =179.79 mg/dl; Post treatment= 120 mg/dl; $p < 0.0001$,with a mean reduction of 33.33%); the mean value of PPBS (Pretreatment= 258.14 mg/dl; Post treatment = 189.60mg/dl; $p < 0.0001$, % fall of 26.47). There was a significant decrease in the mean value of HbA_{1c} as well (Pre treatment =8.82; Post treatment =6.60; $p < 0.0001$, with a mean reduction of 1.6%). Using the frequency intervals and frequency of range, bar diagram was prepared for the mean values of Pre treatment and Post treatment with in Group – 3 (Metformin + Glimepiride).

Figure–6 shows the post treatment values of Metformin(500/1000mg) + Glimepiride (1-4mg) + Pioglitazone (15-30mg) (Group-4) compared to the pre treatment values. There was a significant decrease in the mean value of FBS(Pre treatment =209.37 mg/dl; vs Post treatment= 105.37 mg/dl; $p < 0.0001$, with a mean reduction of 49.67%); a significant decrease in the mean value of PPBS (Pre treatment= 330mg/dl; Post treatment = 170.70mg/dl; $p < 0.0001$,% fall of 48.27%); a decrease in the mean value of HbA_{1c}(Pre treatment =8.95; Post treatment =6.183; $p < 0.0001$,% fall of 1.8%) was observed. Using the frequency intervals and frequency of range, bar diagram was prepared for the mean values of Pre treatment and Post treatment with in Group – 4 (Metformin + Glimepiride + Pioglitazone).

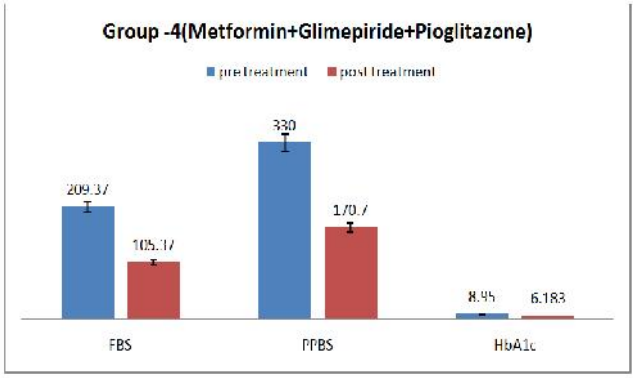

Figure 6: Characteristics of Variables before and after administration of Metformin + Glimepiride + Pioglitazone (Group-4) Drug Therapy (within the same group).

Discussion

The age distribution of our study **(Figure 1)** shows a mean of 53.44 ± 9.15 year's .This denotes the prevalence of the disease at this age group. This goes in alliance to other studies like Bela patel et al 2013, [8] showing a mean age of 56.8±10.5, Adibe Mo et al 2012 with 54.3±13 years. Syed aliul et al [9] 2012 having 56.5±13.2 years with a maximum distribution to 51-60 years age group (52%) similar result obtained by Upadhyay et al [10] 2007 51-60 years with 70% occurance. But Kannan et al [11] got 38.61% occurring in this age group.

Figure 2 shows the distribution of sex in our study. Males were 92 (61.33%) & females were 58 (38.66%). As noticed earlier type II diabetes occurs more in males. Though others like Johnson et al [12] 2006 male 53.1%, Female 46.9% and Yurgin et al[13] 2007 Males-52.6%;Females -47.4%, found males suffering more in number but ratio is not so high. In our study the ratio of M:F (1.5)is higher than Johnson (1.1), Yurgin (1.1)[14]. It may so happen in our case the females are not reporting to the hospital regularly. Mean duration of diabetes observed in this study was 7.8±1.7 years which is comparable with the study of Bela patel 2013, showed that mean duration of diabetes was 8.3 ± 9.4 years and in contrast to the observation made by Upadhyay et al 2007 with a diabetic history of less than 5 years. In our study most of the patients coming within 10 years of disease diagnosis.

Metformin alone and Metformin combination commonly prescribed antidiabetic drug observed in the present study , in line with findings of Johnson et al, Upadhyay et al, Yurgin N et al, Sultana G et al.[15] Glimepiride alone and in combination with metformin were observed in the present study similar to findings of Sultana G et al ,Kannan et al. Metformin + glimepiride was most commonly prescribed combination for diabetes observed in the present study, in line with findings of Bela patel et al, kannan et al. Metformin + Glimepiride + Pioglitazone was most commonly prescribed three drug combination in the present study , in line with findings of sultana G et al, Deepak Nathiya et al.[16]

Figure –3 shows the effects of metformin 500/1000mg. There was a significant decrease in the mean FBS (Pre treatment =165.6 ± 1.81 Vs Post treatment= 135.27±1.77; p = 0.0001).The percentage fall of FBS with Metfomin is 18.31%. This is in accordance with Defronzo et al 1995 showing a reduction of mean FBS from 13.7 ± 0.3 mmol/l to 10.6 ± 0.3 mmol/l with a p value < 0.001.This study shows a fall of 13%. Our study showed a greater fall FBS% as we observed the effect after a longer period 7.8vs 29wks. There was a significant decrease in the mean PPBS (Pre treatment= 248±4.65; vs Post treatment = 207.97±4.65; p = 0.0001) with a mean reduction of 16.14%. This finding related to the study conducted by Hoffman J et al [17] 1997, showed a mean reduction of 14.23% with metformin (2x850mg). There was a significant decrease in the mean HbA_{1c} (Pre treatment =8.733±0.110; vs Post treatment =7.163± 0.08; p <0.0001).

In our study the percentage fall in HbA_{1c} is 1.19% compared with Defronzo et al [18] 1995, setter et al 2003, a fall of 1-2 % (duration of treatment was less than 5 years). The fall in HbA_{1c} is observed only in first 6 months. Gregorio F, Ambrosi F et al, [19] and Menzies DG et al, [20] Dornan TL Heller et al,[21] were concluded that metformin is effective in controlling blood sugar levels. Bela patel et al considered Metformin is safer and cost effective drug. According to Stephanie Aleskow [22] Metformin therapy is well studied, inexpensive and unlikely to cause hypoglycemia and should be used as first line therapy.

Figure 4 - The FBS reduced to 28.53mg/dl with a percentage fall of 17.8. Schade Ds et al, [23] 1998 showed that glimepiride lowers FBS by 46mg/dl with 29% fall. Kanek o T et al [24] also got a similar result with 29% fall. The effect on PPBS shows a similar trend. We got a reduction of 38mg/dl in sugar level compared to Schade et al 1998 who got a reduction of 72mg/ dl. This shows a lesser effect of glimepiride on these subjects difficult to explain. Reasons could be very less number of patients getting the drug (16%), could be due to non strict adherance to therapy as well. There was a significant decrease in the mean value of HbA_{1c} (Pre treatment =7.567mmol/l; Post treatment =7.383mmol/l; p =0.0001) with a reduction of 1%. This finding goes with Schade et al 1998,showed HbA_{1c} lowers by 1.4%.GoldBerg R B et al,[25] Rosenstock et al, [26] and Sonnenberg GE Garg DC et al [27] showed Glimepiride is effectively reduces FBS,PPBS & HbA_{1c}.

Figure –5 compares the efficacy of group-2 (Metformin 500/100mg + Glimeperide 1-4mg) in pre

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and post treatment stages. There was a significant decrease in the mean value of FBS with a fall of 60 mg/dl (33.33%). This is in accordance with sivakumar et al, [28] showing a fall of FBS from 171.8 mg/dl to 107.3 mg/dl (34%). There was a significant decrease in the mean value of PPBS (Pre treatment= 258.20±6.05; Post treatment = 189.83±5.03; p <0.0001) with fall of 26.47%. The same author, showing a fall of 52 mg/dl in PPB (22%). Similar data is obtained in estimation of Hb A1c values as well. Like sivakumar we got a reduction of 1.5% vs 1.6%. Our study period is 5 years or more, where as sivakumar's study is only for 6 months. but it seems that beneficiary effect of decreasing glycosylation is present only in first 4-6 months, as shown by Diana sherifali et al [29] 2010.

Figure–6 shows the effects of Metformin (500/1000mg) + Glimepiride (1-4mg) + Pioglitazone (15-30mg) (Group-4). There was a significant decrease in the mean value of FBS showing 49% reduction. PPBS levels had a fall of 48.27%, and HbA_{1c} 1.8%. Similar findings obtained by Meshram et al.,[30] 2005 with a fall of 41% in FBS.43% fall in PPBS level and 1.6% reduction in HbA_{1c}. There is no significant difference between the group-1 (Metformin) and group-2 (Glimepiride), Zhu et al [31] also opined the same.

In between group-1 (Metformin 500/1000mg) vs group -3 (Metformin 500/1000mg + Glimepiride 1-4mg) percentage of reduction in FBS, PPBS, HbA_{1c} was 18.31% Vs 33.33%, 16.14% vs 26.47%, 1.19% vs 1.5% respectively. These findings were in relation to Hye-Soon Kim, [32] 2014 with percentage reduction of FBS, PPBS, HbA_{1c} of 10.19% vs 25.14%, 17.80% vs 22.36%, 0.8% vs 1.2% respectively. In between group 2 and group-3 (Metformin + Glimepiride) vs group-4 (Metformin + Glimepiride + Pioglitazone) percentage of reduction in FBS, PPBS, HbA_{1c} was 33.33% Vs 49.67%, 26.47%Vs48.27%, 1.5% vs 1.8% respectively. This findings goes with Naganjani, [33] 2014 with percentage of reductions in FBS, PPBS, HbA_{1c} of 10.2%Vs20%, 11.7%Vs32%, 0.9 vs1.2%. In between group -1 (Metformin 500/1000mg) vs group - 4 (Metformin 500/1000mg + Glimepiride1-4mg + Pioglitazone 15-30mg) percentage of reduction in FBS, PPBS, HbA_{1c} was 18.31% Vs 49.67%, 16.14% Vs 48.27%, 1.19%Vs 1.8% respectively. In between Group – 2(Glimepiride1-4mg) vs Group-4 (Metformin 500/1000mg + Glimepiride1-4mg + Pioglitazone15-30mg) percentage of reduction in FBS , PPBS, HbA_{1c} was 17.84% vs 49.67%, 15.12% Vs 48.27%, 1.0%Vs 1.8% respectively.

The three drugs in combination produced marked fall in FBS and PPBS as expected. No comparison found in between one and three drugs combination in this respect. It is obvious that three drugs are given when desired glycemic control is not obtained by one or two drugs combination. (ADA Guidelines)

Conclusion

The present study concludes that both the combinations - Metformin + Glimepiride and Metformin + Glimepiride + Pioglitazone, reduced the FBS, PPBS and HbA_{1c} levels more when compared to the Metformin/Glimepiride (either drug used alone). There is no significant difference between Metformin group and Glimepiride group. Most of the drugs fail to achieve the glycemic control .This emphasizes the fact that patient education and compliance of therapy is urgently needed to prevent or reduce the risk of developing the complications.

Conflict of interest: None declared

Ethical approval: The study was approved by the institutional ethics committee

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