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ADHERENCE TO CLINICAL CARE GUIDELINES FOR CYSTIC FIBROSIS-RELATED DIABETES IN 659 GERMAN/AUSTRIAN PATIENTS

Running title: Multicenter evaluation of medical care for CFRD

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Abstract

Background: In Germany/Austria, data on medical care for cystic fibrosis-related diabetes (CFRD) is limited.

Methods: Anonymized data from 659 CFRD patients were analyzed and compared to the latest ADA/CFF guidelines.

Results: Specialized diabetes clinics were attended less frequently than recommended (3.1 vs. 4.0 times yearly). 7.9% of patients had a complete profile of examinations: diabetes education (44.9%), HbA_{1c} (88.8%), blood pressure (79.5%), BMI (86.5%), lipid status (37.5%), retinopathy (29.9%), microalbuminuria (33.2%), self-monitoring of blood glucose (71.6%). HbA_{1c} and blood pressure were measured less frequently than recommended (2.3 and 2.0 vs. 4.0 times yearly). Overall, guidelines were followed more frequently in children than adults. Contrary to recommendations, not all patients were treated with insulin (77.2 vs. 100.0%). Insulin therapy was initiated earlier in children than adults, but there was still a substantial delay (0.9 vs. 2.7 years after diagnosis, $p<0.001$).

Conclusion: In CFRD patients studied, adherence to care guidelines was suboptimal.

1. Introduction

In clinical practice, treatment of cystic fibrosis-related diabetes (CFRD) is a challenge. CFRD shares some characteristics with the more common type 1 or type 2 diabetes, but it is a separate clinical entity [1-3]. Hence, several aspects of medical care are unique to CFRD. Limited guidance for CFRD treatment is available from the German Diabetes Association [4]. A more detailed description of the management of children and adolescents with CFRD is given by the International Society for Pediatric and Adolescent Diabetes [5]. In 2010, the American Diabetes Association (ADA) in cooperation with the Cystic Fibrosis Foundation and the Pediatric Endocrine Society published the latest comprehensive guidelines on clinical care for CFRD [3].

To avoid diabetes-associated complications, adequate treatment of CFRD in addition to the underlying illness is essential. Considerable evidence from epidemiologic studies, and limited clinical trial data, suggest an association between CFRD and worsening nutritional status, pulmonary function, and mortality in cystic fibrosis (CF) [6-8]. In Germany and Austria, medical care for some patients is provided jointly by specialized CF and diabetes clinics, while others are seen by CF teams with pulmonology or gastroenterology expertise only. To our best knowledge, no evaluation of the current state of medical care specific for CFRD has been performed in Germany and Austria. The benchmarking report from the German cystic fibrosis quality assessment group primarily focuses on CF rather than on diabetes in CF [9,10]. Therefore, we analyzed current treatment for CFRD in specialized diabetes clinics using data from a large German/Austrian diabetes patient registry. Additionally, we evaluated whether medical care for CFRD is in compliance with the latest ADA/CF Foundation guidelines.

2. Materials and methods

2.1 Diabetes patient registry DPV

Since 1995, many specialized diabetes clinics from Germany and Austria have documented prospectively demographic and clinical data of diabetes patients in a standardized computer-based software, called DPV (www.d-p-v.eu). Every 6 months, locally documented data are anonymously transmitted to the University of Ulm. To ensure data plausibility, transmitted data are verified and reported back for corrections in case of inconsistency. For central analyses [1,2,11] and quality assurance, all plausible data are aggregated into a cumulative database. The DPV initiative has been approved by the ethical committee of Ulm University.

Until March 2013, 313,973 patients with any type of diabetes were documented in DPV by 392 centers from Germany or Austria. For this study, patients with CFRD and age at diabetes onset >5 years were considered. The final study population comprised 659 CFRD patients from 119 specialized diabetes clinics. For each patient included, datasets were aggregated over the most recent year of care.

2.2 Medical examinations

The number of visits in diabetes clinics during the last treatment year was evaluated and frequency and completeness of recommended medical examinations were analyzed. We also assessed measurement of hemoglobin A_{1c} (HbA_{1c}), blood pressure, and lipids, monitoring of nutritional status and microvascular complications (retinopathy, microalbuminuria), participation in diabetes education programs and self-monitoring of blood glucose (SMBG). Documentation of at least one serum lipid value (total cholesterol, HDL, LDL, triglycerides) was classified as lipid measurement. Attendance of at least one diabetes education program since onset of diabetes was defined as participation. Data on SMBG was collected by physicians on the basis of memory blood glucose meters and patients' entries in paper or electronic blood glucose diaries. Medical audits in a patient were defined as 'complete', if all recommended examinations were performed at least once during the recent year of care.

2.3 Nutritional status

Nutritional status was assessed by body mass index (BMI), BMI standard deviation score (BMI-SDS), weight-SDS and height-SDS. The latter were calculated using contemporary national reference data from the KiGGS study. For patients ≥18 years, values were extrapolated. Underweight was defined as BMI values below the 10^{th} percentile for age <20 years and for adults as BMI<19 kg/m² [12,13]. The recommended target is a BMI ≥50^{th} percentile for age <20 years, and in adults a BMI ≥22 kg/m² for females and ≥23 kg/m² for males [3].

2.4 Metabolic control and anti-hyperglycemic therapy

Metabolic control was assessed by HbA_{1c}. The multiple of the mean method was applied to mathematically standardize HbA_{1c} values to the DCCT reference range (20.7-42.6 mmol/mol) [11]. An HbA_{1c} ≤53 mmol/mol (≤7.0%) is recommended for most CFRD patients [3]. Anti-hyperglycemic therapy was specified as: i) insulin treatment (insulin only or with additional glucose lowering agents), ii) oral anti-diabetic drug (OAD) medication and iii)

non-pharmacological treatment (dietary/physical advice only). Insulin therapy was categorized as basal insulin only, conventional treatment (CT, 1-3 injection time-points/day), multiple-daily injections (MDI, 4-8 injection time-points/day) or continuous subcutaneous insulin infusion (CSII). Daily insulin dose per kilogram bodyweight was calculated.

2.5 Statistical analysis

SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) was applied for data analysis. For each recommended examination, frequency of patients with at least one measurement during the recent treatment year was calculated. For examinations recommended more than once yearly (HbA_{1c}, blood pressure), the respective number of measurements within the last year was analyzed. Daily frequency of SMBG was evaluated. Results were displayed as mean with 95% confidence interval for continuous variables and as percentage for dichotomous variables.

Besides analysis of the whole study population, gender- and age-specific analyses were carried out. Study population was divided into two age groups: <20 (pediatric) and ≥20 years (adult).

Continuous parameters were compared using Kruskal-Wallis test. χ^2-test was applied for dichotomous variables. A two-sided $p<0.05$ was considered significant.

All results were compared to the latest ADA/CF Foundation clinical care guidelines for CFRD [3].

3. Results

3.1 Study population

Baseline characteristics, stratified by gender and age group, are given in Table 1. 58.4% of study population were female and 54.2% were younger than 20 years. Females were younger, taller and had an earlier onset of CFRD compared to males ($p<0.001$), but otherwise there were no difference in gender at baseline. However, several significant differences were noted between age groups, including later age at diagnosis, longer duration of diabetes, and better nutritional status in adults. For 59.6% of patients, medical care was provided by diabetes clinics with >10 CFRD patients.

3.2 Medical examinations

Table 2 displays the observed frequency and number of examinations in CFRD compared to guideline recommendations. The percentage of patients with complete examinations is given.

In specialized diabetes clinics, patients were seen less frequently than recommended. Only 7.9% of patients had a complete profile of examinations. 44.9% of patients had at least one structured diabetes education program since the onset of diabetes.
Not all patients received the recommended measurements of HbA_{1c}, blood pressure or lipids and the advised assessment of nutritional status or monitoring of microvascular complications at least once during the recent year of care. In patients with measured HbA_{1c} or blood pressure, the yearly number of measurements was lower than recommended.
SMBG was performed in 71.6% of patients only. On average, patients performing SMBG achieved the recommended frequency of 3 measurements per day.

Pediatric patients visited diabetes clinics significantly more often than adults (Table 2). In general, the frequency and number of recommended examinations was significantly higher in younger patients, except for lipid measurements and retinal examinations. Hence, medical audits were complete in significantly more pediatric patients than adults. Daily frequency of SMBG was comparable between age groups.
Overall, between genders, no significant differences were observed.

3.3 Nutritional status

BMI, BMI-SDS, weight-SDS and height-SDS for all patients and stratified by gender or age are given in Table 1. In 36.5% of patients weight was below the 3rd percentile for age and sex. A height below the 3rd percentile was observed in 24.7% of patients. Underweight was present in 38.4% of patients and was significantly more prevalent in children and adolescents (Table 1). 16.7% of patients achieved the recommended BMI target (Fig. 1a). In adults, BMI achievement was significantly more prevalent than in younger patients (Fig. 1a). Between genders, prevalence of underweight and achievement of BMI target did not differ (Table 1, Fig. 1a).

3.4 Metabolic control and anti-hyperglycemic therapy

Mean HbA_{1c} during the last year of care was 55 (95% CI: 54 – 57) mmol/mol (7.2 (7.1 – 7.4)%). 58.6% of patients had an HbA_{1c} below or equal to the recommended target, with no differences between genders or age groups (Fig. 1b).
Contrary to recommendations, not all patients were on insulin (Fig. 2). 6.7% of patients were treated with OADs only and 16.1% received non-pharmacological therapy. Anti-hyperglycemic therapy did not differ significantly between genders or age groups (Fig. 2).

Independent of gender or age group, multiple-daily injections was the preferred insulin regimen (Table 3). 5.7% of insulin-treated patients used basal insulin only, with no significant differences between genders or age groups (Table 3). Daily insulin dose per kg body weight was higher in pediatric patients than adults, but comparable between genders (Table 3).
On average, insulin therapy was initiated 1.7 (1.4 – 2.0) years after diagnosis of diabetes. In pediatric patients, time to insulin treatment was significantly shorter than in adults, but there was still a substantial delay (0.9 (0.7 – 1.1) vs. 2.7 (2.1 – 3.3) years; $p<0.001$). Between genders, no difference was observed (males vs. females: 1.9 (1.4 – 2.3) vs. 1.6 (1.3 – 2.0) years; $p=0.48$).

4. Discussion

Beside the German benchmarking reports, which focus on CF rather than on diabetes in CF, this is the first study evaluating current state of medical care specific to CFRD in Germany and Austria. Compared to the latest ADA/CF Foundation guidelines, our study revealed a lack of adherence to current international clinical care guidelines for the CFRD population studied. Multidisciplinary treatment by CF and diabetes experts with good team communication and consistent instructions regarding diabetes care, as well as more data regarding benefits of CFRD treatment, might improve adherence to published guidelines.

Manifestation of diabetes most commonly occurred at an age where patients were at the transition from pediatric facilities to departments of internal medicine. This might be an additional confounder that makes adequate treatment of CFRD difficult. A loss in transition from pediatric to adult care has been described for patients with type 1 diabetes [14], and may play a role in CFRD. Patients may feel more comfortable in pediatric clinics, and thus more likely to follow recommendations, because they have attended these centers regularly since CF diagnosis. Moreover, pediatricians might be more aware of secondary diabetes as CF comorbidity than specialists in internal medicine.

In German/Austrian diabetes care centers, more than half of patients had never participated in a structured diabetes education program since onset of diabetes. This might be due to concerns about bacterial colonization or insufficient time as multiple CF-related therapies are required. Additionally, education topics differ between CFRD and type 1 or type 2 diabetes (e.g. low rate of ketoacidosis, high-calorie diet, relevance of microvascular complications vs.

risk of lung infections). In CFRD, an individualized education with CF-specific training material is necessary. In contrast to other types of diabetes, the underlying disease in CFRD is life-threatening; hence, psychological counseling is also different.

Even though HbA_{1c}, BMI and blood pressure were measured at least once during the recent year of care in the majority of patients, lipid status and microvascular complications were monitored in a minority of patients only. Perhaps there are concerns or doubts about the utility of these measurements in long-term outcomes of CF patients, including lack of strong evidence behind some of the guideline recommendations in the CFRD population. In the case of lipid and retinopathy screening, logistical implications may play a role (e.g. fasting conditions for lipid measurement, or specialist referral for retinopathy screening). In general, pediatric patients received medical examinations more often than adults. Children and adolescents may visit medical centers more frequently than adults. Moreover, some examinations (like BMI, lipid status) may seem less important in adulthood, when little year-to-year variation is expected.
HbA_{1c} and blood pressure were measured only half as often as recommended. These measurements may also be performed by CF clinics and thus intentionally not duplicated in specialized diabetes clinics. Nevertheless, diabetes clinics should be aware of the results to include them in their longitudinal documentation for appropriate long-term care. Recently, data documentation in the DPV software has been expanded to include lung function parameters (FEV_1, vital capacity) and type of CFTR mutation. In parallel, the German CF quality assessment group added the documentation of further diabetes-related parameters to their CF registry [9,10]. A more interdisciplinary approach, as recommended by guidelines [3], may facilitate improved screening and treatment.

About one third of patients had a metabolic control worse than recommended. In type 1 or type 2 diabetes, the HbA_{1c} target is also not achieved by many patients [15-17]. In the latest National Health and Nutrition Examination Survey, only 52.5% of adults with diabetes had an HbA_{1c} <7% [18]. HbA_{1c} is the preferred indicator of glycemic control in type 1 or type 2 diabetes [19]. In CFRD, HbA_{1c} values are often falsely low due to an increased hemolysis in CF [20,21]. In addition, acute and chronic infections may contribute to higher values. The degree of metabolic control documented in this study is ‘optimistic’. Assuming that at least some HbA_{1c} values were falsely low, the true number of patients with poor metabolic control is likely higher than the one-third estimate mentioned. As in other forms of diabetes, an

elevated HbA_{1c} in CFRD is associated with an increased risk of microvascular complications [22]. Hence, monitoring HbA_{1c} regularly is appropriate in order to observe trends in glycemic control [3].

Loss of calories through malabsorption and high resting energy expenditure often contribute to a poor nutritional status in CFRD. Less than 20% of patients had a BMI equal to or above the target. Compared to adult CF patients (≥18 years) from the German CF benchmarking reports in 2001 and 2008 [9,10], our adult CFRD patients (≥20 years) revealed on average a comparable BMI, but a lower height-SDS. Weight-SDS and height-SDS of our pediatric CFRD patients (<20 years) were lower than in pediatric CF patients (<18 years) from the benchmarking report in 2001 [9]. A poor nutritional status is associated with declining lung function and increased mortality. Especially in pediatric patients, additional energy requirement for growth should be kept in mind. In CFRD, different dietary advice is necessary compared to type 1 or type 2 diabetes.

The only recommended pharmacologic therapy for CFRD is insulin [3]. OADs are not advised, because they showed less effectiveness and are less well studied in CFRD [3]. As shown in this study, in clinical practice not all patients are treated with insulin. In a questionnaire survey among UK CF centers, insulin was the preferred treatment modality in 97% of investigated centers [23]. In contrast to our analysis, pediatric centers in the UK used OADs less frequently than departments of internal medicine.
Our data further indicate that insulin therapy was not initiated immediately after the diagnosis of diabetes in all patients. However, an earlier start of insulin therapy in younger patients compared to adults was observed. There is little evidence on the optimal insulin regimen in CFRD [3]. In our study, the majority of patients preferred multiple-daily injections. Improvements of lung function, nutritional status and metabolic control as well as decreasing mortality were reported as benefits of insulin therapy in CFRD [24-27].

The reasons for withholding insulin treatment remain unclear. Patients in an early stage of CFRD may not be persistently hyperglycemic. Furthermore, the start of insulin treatment might be considered as an additional burden for patients, who already require multiple CF-related therapies and often face social challenges around the age of CFRD onset (e.g. increasing autonomy, moving out of the family home, starting work). By comparison, oral anti-diabetic treatment or lifestyle intervention may be less complex or labor-intensive for

both providers and patients. In addition, the fear of insulin-induced hypoglycemia may play a role. In CFRD, insulin-induced hypoglycemia may be aggravated by decreased hepatic glycogen stores and impaired pancreatic glucagon secretion. Moreover, screening practices for CFRD and administration of insulin therapy in CFRD with and without fasting hyperglycemia have changed over the years [3,28]. This may account also for the longer delay in instituting insulin therapy in adults compared to children, who presumably were diagnosed more recently. Nowadays, an oral glucose tolerance test is recommended for every CF patient aged ≥10 years and all CFRD patients, independent of fasting blood glucose, should receive insulin [3]. In a multicenter study, conducted between 2001 and 2010, serial oral glucose tolerance tests were performed by 43 specialized CF centers from Germany and Austria [29], indicating that regular screening is becoming more widespread in this region.

Strengths of our study include its large number of patients from various parts of Germany/Austria, the standardized documentation of clinical data by trained medical staff and the rigorous analysis of a large medical database rather than relying on questionnaires. A limitation is that only specialized diabetes centers were included. Indeed, CFRD patients also visit CF specific clinics. Therefore, the total number of visits to medical care centers is probably higher than documented in our study. Nevertheless, as diabetes-specific examinations likely are completed less often in CF clinics compared to specialized diabetes centers, the true adherence to guidelines in CFRD patients might be even lower than reported here.

Conflict of interest statement

The authors have no conflicts of interest relevant to this work to disclose.

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Table 1. Baseline characteristics of study population.

	All	Male	Female	P-value	<20 years	≥20 years	P-value
Number of patients, n	659	274	385	-	357	302	-
Females, %	58.4	0.0	100.0	-	60.8	55.6	NS
Age, years	22.9 (22.0 – 23.7)	24.0 (22.7 – 25.4)	22.0 (21.0 – 23.0)	0.010	16.3 (16.1 – 16.6)	30.5 (29.3 – 31.8)	<0.001
Age at diagnosis, years	18.8 (18.1 – 19.5)	19.9 (18.8 – 21.1)	18.0 (17.1 – 18.9)	<0.001	13.9 (13.6 – 14.2)	24.6 (23.3 – 25.8)	<0.001
Duration of diabetes, years	4.0 (3.7 – 4.4)	4.1 (3.4 – 4.7)	4.0 (3.6 – 4.5)	NS	2.4 (2.2 – 2.7)	6.0 (5.3 – 6.7)	<0.001
BMI, kg·m^{-2}	19.5 (19.2 – 19.8), n=570	19.7 (19.3 – 20.1), n=229	19.4 (19.0 – 19.7), n=341	NS	18.7 (18.4 – 18.9), n=328	20.6 (20.2 – 21.1), n=242	<0.001
BMI-SDS	-1.0 (-1.1 – -0.9)	-1.0 (-1.2 – -0.9)	-1.0 (-1.2 – -0.9)	NS	-1.2 (-1.3 – -1.1)	-0.8 (-1.0 – -0.7)	0.004
Weight-SDS	-1.5 (-1.7 – -1.4), n=597	-1.6 (-1.8 – -1.4), n=239	-1.5 (-1.7 – -1.1), n=358	NS	-1.8 (-2.0 – -1.6), n=333	-1.2 (-1.4 – -1.0), n=264	<0.001
Height-SDS	-1.0 (-1.1 – -0.9), n=583	-1.2 (-1.3 – -1.0), n=236	-0.9 (-1.0 – -0.8), n=347	0.015	-1.2 (-1.3 – -1.0), n=333	-0.8 (-0.9 – -0.7), n=250	<0.001
Underweight, %	38.4	38.9	38.1	NS	42.1	33.5	0.037
Systemic steroids, %	19.4	20.4	18.7	NS	22.1	16.2	NS

Data are given as mean with 95% confidence interval or as percentage. P-values are given for the comparison between genders or age groups.

Abbr.: *BMI* body mass index, *SDS* standard deviation score, *NS* not significant.

Table 2. Medical examinations in German and Austrian patients with CFRD compared to guidelines [3].

	Guideline	All	Male	Female*	<20 years	≥20 years	P-value
Visits, per year	4.0	3.1 (3.0 – 3.3)	3.0 (2.8 – 3.3)	3.2 (3.0 – 3.5)	3.5 (3.2 – 3.8)	2.7 (2.5 – 3.0)	<0.001
At least one recommended examination:							
Diabetes education program since onset, %	100.0	44.9	42.3	46.8	51.8	36.8	<0.001
HbA_{1c}, %	100.0	88.8	88.3	89.1	91.6	85.4	0.012
SMBG, %	100.0	71.6	71.2	71.9	76.8	65.6	0.002
BMI, %	100.0	86.5	83.6	88.6	91.9	80.1	<0.001
Blood pressure, %	100.0	79.5	78.5	80.3	82.4	76.2	0.049
Lipid status, %	100.0	37.5	35.8	38.7	40.1	34.4	NS
Retinopathy, %	100.0	29.9	27.7	31.4	31.4	28.1	NS
Microalbuminuria, %	100.0	33.2	32.8	33.5	37.8	27.8	0.007
Complete examinations, %	100.0	7.9	8.0	7.8	10.6	4.6	0.004
Examinations recommended more than once:							
HbA_{1c}, per year	4.0	2.3 (2.1 – 2.4)	2.2 (2.0 – 2.5)	2.3 (2.1 – 2.5)	2.6 (2.4 – 2.8)	1.9 (1.8 – 2.1)	<0.001
Blood pressure, per year	4.0	2.0 (1.9 – 2.2)	1.9 (1.7 – 2.2)	2.1 (1.9 – 2.3)	2.3 (2.1 – 2.6)	1.6 (1.5 – 1.8)	<0.001
SMBG, per day	3.0	3.3 (3.2 – 3.5)	3.3 (3.0 – 3.5)	3.4 (3.2 – 3.5)	3.3 (3.1 – 3.5)	3.4 (3.2 – 3.6)	NS

Data as mean with 95% confidence interval or as percentage. P-values are given for the comparison between age groups. *indicate that for all comparisons between genders difference was not significant. Abbr.: *BMI* body mass index, *HbA_{1c}* hemoglobin A_{1c}, *NS* not significant, *SMBG* self-monitoring of blood glucose.

Table 3. Type of insulin regimen and insulin dose per kilogram bodyweight in insulin-treated patients with CFRD.

	All	**Male**	**Female**	P-value	**<20 years**	**≥20 years**	P-value
Number of patients, n	509	209	300	-	281	228	-
Basal insulin only, %	5.7	5.7	5.7	NS	6.8	4.4	NS
Conventional treatment, %	40.9	42.6	39.7	NS	39.1	43.0	NS
Multiple-daily injections, %	53.6	50.7	55.7	NS	54.4	52.6	NS
CSII, %	5.5	6.7	4.6	NS	6.5	4.4	NS
Daily insulin dose, IU/kg	0.78 (0.73 – 0.83), n=482	0.74 (0.66 – 0.82), n=192	0.81 (0.75 – 0.87), n=290	NS	0.85 (0.78 – 0.92), n=273	0.69 (0.62 – 0.76), n=209	0.002

Data are given as mean with 95% confidence interval or as percentage. P-values are given for the comparison between genders or age groups.

Abbr.: *CSII* continuous subcutaneous insulin infusion, *NS* not significant.

Fig. 1. Percentage of patients achieving target for (A) BMI or (B) HbA_{1c}.

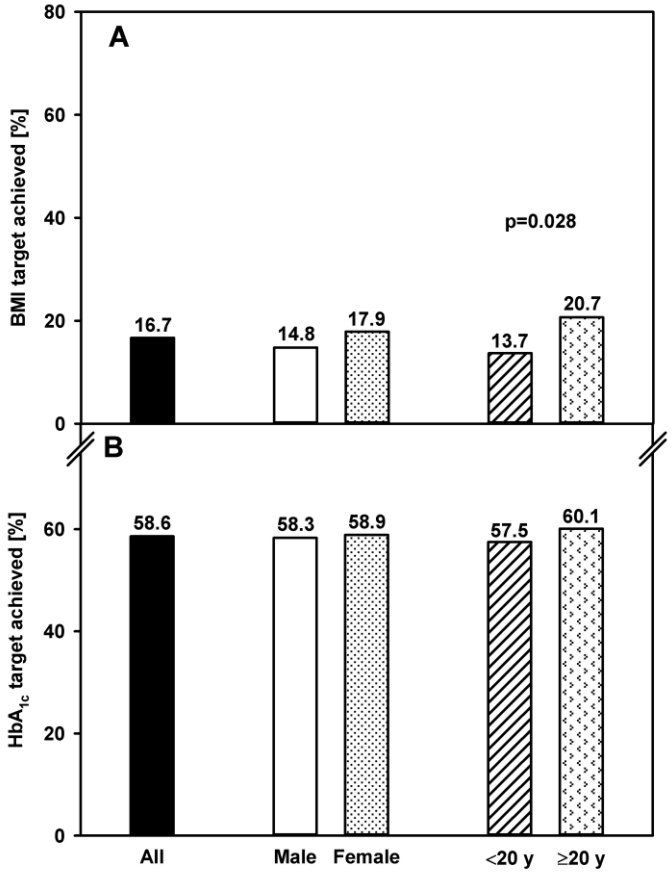

Fig. 2. Anti-hyperglycemic therapy compared to guidelines [3].