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Implementation in a Family Medicine Clinic of a Lifestyle Program Designed to Help Indigent, Obese Adult Patients Lose Weight

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ABSTRACT

Introduction. Efficacy of interventions in research settings may not translate to usual-care settings. The impact of interventions varies depending upon factors, such as the proportion and composition of the population reached and engaged, as well as participation and implementation characteristics of providers.

Methods. A lifestyle intervention meant to achieve a 5% loss of body weight in six months was offered to obese, indigent adult patients in a Family Medicine residency outpatient clinic. Implementation variables were assessed, including determination of individual patient penetration and participation rate, demographic representativeness, completion rate, outcomes, and differential impact, as well as setting participation rates and implementation fidelity.

Results. From a population of 743 potentially eligible patients, 356 were invited to participate (48% penetration) and 158 were enrolled (44% participation). Those enrolled were heavier (BMI of 42.6 vs 39.0), younger (43.5 vs 47.0 years) and more likely female (87% vs 69%) than those not enrolled. Individual completion rate was 81%; overall weight loss was negligible. Setting participation was broad, but fidelity to background standard of care was only 50%.

Conclusions. Providers were eager for a tool to help their obese, indigent patients lose weight, but the intervention proved ineffective and the usual care of enrolled patients was not strongly supportive of their weight loss efforts. ***KS J Med 2016;9(4):77-82.***

INTRODUCTION

In the United States, 26.9% of adults are obese (i.e., have a body mass index greater than 30.0) and, in Kansas, 28.8% of adults are obese, putting them at high risk for diabetes.[1] The United States Preventive Services Task Force (USPSTF) has recommended that "Clinicians should offer or refer patients with a body mass index of 30 kg/m2 or higher to intensive, multicomponent behavioral interventions (B recommendation)."[2]

Initiatives such as the Diabetes Prevention Program (DPP) based on the three tenets of increased physical activity, nutrition, and social support have been effective in promoting lifestyle change and weight loss, and ultimately preventing diabetes.[3,4] Extensions of the DPP into community settings, such as the YMCA, have shown efficacy can be transported into wider populations.[5] However, even the most promising intervention can be undermined by weak implementation. A review of implementation of 38 DPP-style programs concluded that program intensity plays a major role in weight loss outcomes.[6] Programs that have high uptake, both in terms of good coverage of invitees and their willingness to accept the invitation, can have considerable impact in lowering diabetes risk in a population, even with a low intensity intervention that only leads to low or moderate weight loss. This is an important finding for resource-constrained settings.

Primary care physicians in our residency outpatient clinic care for an economically disadvantaged clinical population with a high rate of obesity. In this time- and resource-constrained setting, physicians were eager to find simple and affordable options for patients to lose weight and prevent diabetes. Given that the effectiveness of primary care delivered weight loss programs has been demonstrated among adults with socioeconomic disadvantages,[7] we chose to provide a practical, simplified DPP-style program to our indigent clinic patients who were obese and at the highest risk for diabetes.[8,9] A separate report will detail the intervention and its efficacy. This report describes the clinical aspects of implementation of the program within a large Family Medicine residency outpatient clinic using metrics derived from the models RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance)[10] and PIPE (Penetration, Implementation, Participation, Effectiveness).[11]

METHODS

Participants. The program was designed by faculty of a large Family Medicine residency program to assist obese, indigent clinic patients with weight loss. Obese (body mass index [BMI] ≥ 30 kg/m2), indigent (≤ 200% Federal Poverty Level, FPL) adults (age 18 - 70) without contraindications to weight loss were included. Potential participants were identified on daily reports of scheduled patients (based on age and most recent BMI); patients scheduled acutely were occasionally added to the list when identified by clinic staff. Patients were approached at clinic visits regarding study participation by physicians or staff. Staff of the eight clinic teams referred interested patients to the study coordinator for additional screening and enrollment of eligible participants willing to provide informed consent. Indigency was determined first from insurance coverage: Medicaid and forms of charity care indicate an income of < 200% FPL. For individuals who were insured privately or on Medicare, self-report of income was considered in the context of household size; for a family of four, 200% FPL is $47,100. The protocol was approved by the Via Christi Institutional Review Board.

Lifestyle Program. Participants consented to a no-cost, one-year lifestyle intervention program, comprised of a six-month acute phase in which the goal was a 5% loss in body weight, followed by a six-month maintenance phase in which the goal was retention of weight loss.

Participants were offered a pedometer, a coupon good for a pair of athletic shoes and socks, and their choice of either a membership to the YMCA or an exercise prescription.

Nutrition was addressed by offering a choice of three simplified "diet plans". The first ("meal plan") was centered on limiting calories to 900 to 1000 per day. The meal plan limited daily intake to two 11 oz. bottles of SlimFast©, one Healthy Choice© or Lean Cuisine© frozen meal, a piece of fruit, and another 100-cal snack. A second option ("50% diet") was based on portion size and "simply eating half of whatever you have been eating". The final plan ("5210") is based on the 5210 plan used by Let's Go Childhood Obesity Program (http://www.letsgo.org) and involves eating 5 fruits and vegetables per day, limiting "screen time" to 2 hours, engaging in 1 hour of physical activity, and having 0 sugared drinks and desserts in the house.

Social support was in the form of a weekly call from a study coordinator, whose function was to provide a means of accountability, assistance in identifying barriers and solutions, and communication with the study investigators and clinic team. The primary outcome was six-month change in body weight; secondary outcomes were blood glucose or HgbA1c levels at six months and maintenance of weight loss in the following six months.

Standard of Care. The lifestyle program was approved as research intended to operate in the context of the clinic's self-defined Standard of Care for patients with or at risk of diabetes who have made a commitment to lose weight and require focused visits to achieve that end. This Standard includes visits to evaluate and counsel on the patient's progress scheduled at one month, three months, six months, nine months, and one year following initial evaluation, and measurement of HbA1c levels at baseline and one year. Weight, vital signs, and laboratory data were extracted from the patient's medical record, as were any visit notes pertinent to counseling on physical activity or nutrition.

Data Analysis. The concept of Reach[10] was used to describe what proportion of the target population was enrolled in the study (individual participation rate) and how well they represented the eligible clinic population (demographic representativeness). Reach was described as the proportion of eligible clinic patients invited (penetration) and the proportion of invited patients enrolled (participation).[11] Effectiveness was described in terms of individual completion rate, categorical outcomes, and differential impact of sex and age for participants and subgroups of participants who completed each phase (six-month acute; six-month maintenance). Adoption was evaluated in terms of setting participation rates of clinic providers and implementation in terms of fidelity to Standard of Care protocols by clinic providers. Descriptive statistics were used to characterize the population, inferential statistics (analysis of variance, chi-square) to compare groups statistically, and effect sizes (ES; Cohen's d, partial eta squared, Pearson correlation coefficient, or phi) to estimate clinical significance. Analyses were conducted in SPSS 19; $p < .05$ was used to define statistical significance.

RESULTS

Reach. The pool of potential participants was formed from a total of 832 patients: 784 pre-scheduled patients whose weight history and age met inclusion criteria and 48 patients scheduled acutely and deemed evaluable by clinic staff. Study criteria excluded 89, leaving 743 patients potentially eligible (unless qualified by virtue of Medicaid insurance, indigency could not be assessed except through screening). We invited 356 (for a penetration of 48%) and enrolled 158 (for participation of 44%); the resultant individual participation rate was 21% (158/743; Figure 1). Demographic representativeness was evaluated by comparing potentially eligible patients subsequently enrolled with those not enrolled (Table 1).

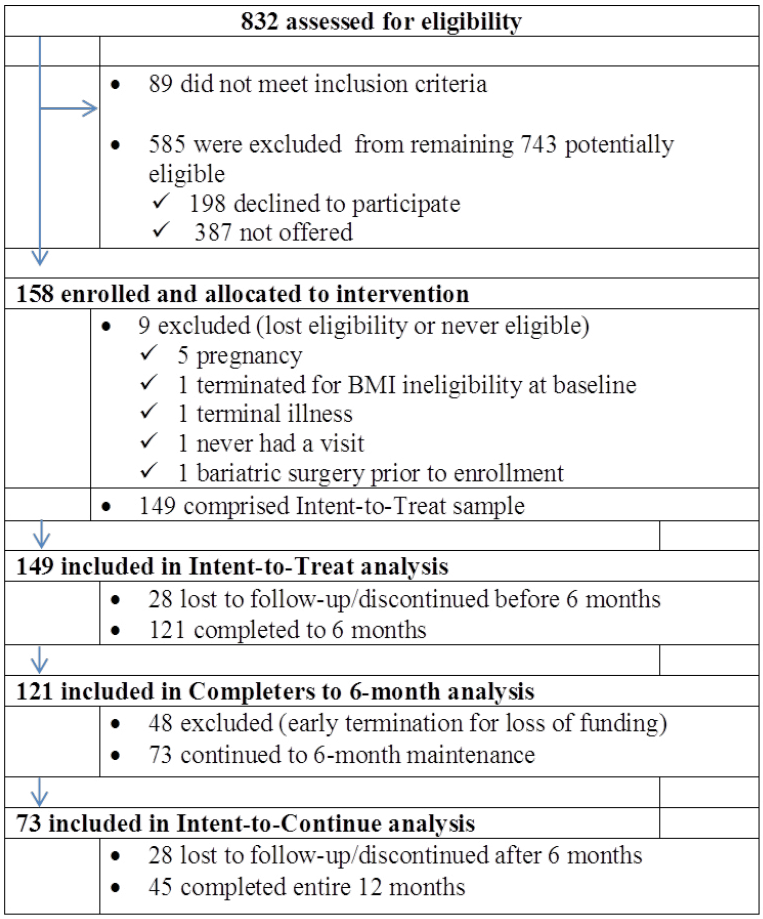

Figure 1. Participant flow.

Enrolled subjects, relative to non-enrolled, were heavier (BMI = 42.6 vs 39.0; ES = 0.43, $p < .01$), younger (43.5 vs 47.0; ES = 0.27, $p < .01$), and more likely to be female (87% vs 69%; ES = 0.16, $p < .01$). Enrolled subjects also were more likely to be solicited through active agency of the clinic rather than the daily report of pre-scheduled patients (18% vs 2%; ES = 0.28, $p < .01$). Enrolled and non-enrolled patients did not differ in racial distribution (ES = 0.07, $p > .10$) or in diagnosis of diabetes or other relevant diagnosis (ES = 0.05, $p > .10$).

There was a tendency for insurance indicating indigency (Medicaid or no insurance) to be found more often among enrollees (68.4% vs 61.0%; ES = 0.06, p < .10). Disability (defined as Medicare insurance prior to age 65) did not differ between patients who were enrolled and those not enrolled.

Table 1. Demographic characteristics of potentially eligible patients subsequently enrolled or not enrolled (n = 743).

		Enrolled n = 158		Not Enrolled n = 585		Effect Size	p
		Mean	S.D.	Mean	S.D.		
Age		43.5	11.9	47.0	13.8	0.27	< **.01**
BMI		42.6	8.9	39.0	7.7	0.43	< **.01**
		n	%	n	%		
Sex	Female	137	86.7	403	68.9	0.16	< **.01**
	Male	21	13.3	182	31.1		
Race	White	97	61.4	394	67.4	0.07	> .10[a]
	Black	52	32.9	174	29.7		
	Other	9	5.7	17	2.9		
Diagnosis	Diabetes Mellitus	44	27.8	208	35.6	0.05	> .10[b]
	Other Relevant Diagnosis[c]	4	2.5	0	0		
	No Relevant Diagnosis	110	69.6	377	64.4		
Source	Daily Report	129	81.6	571	97.6	0.28	< **.01**
	Added Patients	29	18.4	14	2.4		
Insurance	Medicaid Only	64	40.5	218	37.3		
	Medicaid + Medicare	30	19	115	19.7		
	Uninsured	14	8.9	24	4.1		
	Commercial	20	12.7	111	19.0		
	Medicare Only	12	7.6	85	14.5		
	Unknown	18	11.4	32	5.5		
Indicating Indigence[d]							
	Yes	108	68.4	357	61.0	0.06	< .10
	No	50	31.6	228	39.0		
Indicating Permanent Disability[e]							
	Yes	40	25.3	154	26.3	0.01	> .10
	No	118	74.7	431	73.7		

[a]white vs. non-white
[b]diabetes mellitus or other relevant diagnosis vs. no diagnosis
[c]other relevant diagnosis: antepartum diabetes, dysmetabolic syndrome X (2), abnormal glucose
[d]insurance indicating indigency (Medicaid, uninsured) vs. not (commercial, Medicare only, unknown)
[e]insurance indicating disability (Medicare received before 65 years) vs. not

Effectiveness. Of 158 participants enrolled, eight were excluded from analysis because they were or became ineligible and one was excluded because of no visits, thus no data. Among the 149 participants who could have completed through six months, 28 were lost to follow-up or discontinued prior to six months for an individual completion rate of 121/149 or 81%.

Average weight loss over six months was small among the 121 completers (0.28 lb, ES = 0.18). Average loss was 0.5% of body weight at one month, 0.5% body weight at three months, and 0.1% at six months. When outcomes were classified against the goal of achieving 5% loss of body weight at six months, 18 (14.9%) were successful, 12 (9.9%) gained 5% of body weight, and 91 (75.2%) changed by less than 5% (Table 2).

Table 2. Weight outcomes overall, by sex, by age quartile completers to 6 months (n = 121).

		n	%		
Overall					
6 month status	5% loss	18	14.9		
	< 5% change	91	75.2		
	5% gain	12	9.9		
		Mean	S.D.	Effect Size	p
Pounds lost at 6 months		0.3	12.0	0.18	> .10
Subgroup Analyses					
Pounds lost	women, n = 102	0.3	10.1		> .10
	men, n = 19	3.4	19.2		> .10
Pounds lost	18-36 years	-5.2	14.2	0.11	.07
	36-46 years	1.0	10.1		> .10
	46-53 years	0.1	8.8		> .10
	53-65 years	4.5	13.0	0.11	.07

Differential impact of sex and age was assessed in six-month completers. Weight did not change over time in subgroups defined by sex (ES < 0.04, p > .10). Trends (ES = 0.11, p = .07) toward weight gain in the youngest age quartile and weight loss in the oldest were noted. Subsequent correlation analysis indicated that increasing age was related positively to weight loss (ES = .23, p < .05), and more so in men (ES = .47, p < .05) than in women (ES = .16, p > .10).

Maintenance. Loss of funding led to early termination of 48 of 121 completers to six months. The remaining 73 subjects were included in the Intent-to-Continue analysis. The individual completion rate to one year in the maintenance phase was 62% (45 of 73).

The 45 completers-to-one-year had average gains (vs baseline) of 0.4% body weight at six months and 0.1% at one year. Nevertheless, when outcomes were classified as the proportion achieving 5% loss of body weight, 5 (11.1%) were successful at six months and 10 (22.2%) were successful at one year. There were no differences within sex or within age quartiles in weight across maintenance visits (Table 3).

Table 3. Weight outcomes overall, by sex, by age quartile completers to 12 months (n = 45).

		n	%		
Overall					
1 year status	5% loss	10	22.2		
	< 5% change	28	62.2		
	5% gain	7	15.6		
		Mean	S.D.	Effect Size	p
Pounds lost	6 months	-1.2	11.7		
	12 months	0.0	15.5	0.02	> .10
Subgroup Analyses					
Pounds lost	women, n = 38	-0.7	10.1		> .10
	men, n = 7	1.0	19.9		> .10
Pounds lost	18-36 years	-4.2	18.3		> .10
	36-46 years	-2.2	13.4		> .10
	46-53 years	-0.5	13.7		> .10
	53-65 years	6.7	15.0		> .10

Adoption. Setting participation was distributed broadly across residents and teams. The majority of residents on each team were active in enrolling patients; all residents but one or two per team enrolled at least one patient. Study information was offered to 52 - 63% of potentially eligible patients at Clinic 1; at Clinic 2 the range was 21 - 44%. Ultimately, Clinic 1 enrolled 16 - 24% of their potentially eligible patients; at Clinic 2 the range was 13 - 28% (Table 4).

Table 4. Outcomes by team and clinic: Adoption of program.

Clinic 1			Clinic 2	
# residents enrolling/# residents				
team 1	5/6	83%	6/7	86%
2	5/6	83%	5/7	71%
3	6/8	75%	6/7	86%
4	5/7	71%	5/7	71%
# solicited/# opportunities				
team 1	63/111	57%	22/68	32%
2	54/103	52%	13/63	21%
3	79/126	63%	38/87	44%
4	64/102	63%	23/83	28%
# enrolled/# opportunities				
team 1	27/111	24%	9/68	13%
2	25/103	24%	9/63	14%
3	30/126	24%	24/87	28%
4	16/102	16%	18/83	22%

Implementation. Usual care visits during the first six months were evaluated for implementation of Standard of Care procedures (Table 5).

Table 5. Outcomes by team and clinic: Implementation of Standard of Care components.

Clinic 1			Clinic 2	
# visits in first 6 months (median, range)				
team 1	3	(1 - 4)	4	(3 - 4)
2	3	(2 - 4)	4	(3 - 4)
3	4	(2 - 4)	4	(2 - 4)
4	4	(2 - 4)	4	(3 - 4)
% completed visits with dietary counsel documented (median, range)				
team 1	0	(0 - 100)	50	(0 - 50)
2	0	(0 - 75)	25	(0 - 50)
3	0	(0 - 75)	25	(0 - 100)
4	0	(0 - 33)	33	(0 - 75)
% subjects with HbA1c or glucose within first month				
team 1	41		83	
2	65		43	
3	67		70	
4	54		58	
Standard of Care scores and ranks[a]				
team 1	1.75	51.9	2.39	82.8
2	1.74	46.8	1.90	56.6
3	1.97	60.3	2.35	78.8
4	1.65	48.3	2.26	75.1

[a]Standard of Care Score: Sum of proportion fidelity to 4 standards of care [% expected visits; % visits with documentation on nutrition, % visits with documentation on activity; HbA1c or glucose obtained by 1 month; Maximum score = 4, average rank = 61]

Most subjects (70/121) completed the expected four visits in six months. About half (61/121) had no documentation of dietary counseling at any visit, and most (74/121) had documentation of exercise counseling at no more than one visit. Laboratory values were examined, showing that most subjects (72/121) had either HbA1c or glucose drawn by the one-month visit.

For each subject completing six months, a Standard of Care Score (maximum value = 4) was derived by summing (1) proportion of four visits completed; (2) whether (= 1) or not (= 0) HbA1c or glucose was obtained by one month; (3) proportion of visits with documentation of dietary counseling; and (4) proportion of visits with documentation of exercise counseling. The median Standard of Care score was 2.0 (IQR: 1.5 to 2.5), thus the component implementation rate was 2.0/4 = 0.5. Post-hoc analysis of ranked scores revealed a substantial effect of clinic on Standard of Care score (means of 52.8 vs 74.9; $p < .01$; ES = 0.66).

DISCUSSION

The clinical goal of helping indigent, obese patients lose 5% of body weight in six months was not realized. Average weight loss in completers to six months was only 0.1%. Aspects of program implementation that may have affected the odds of success were identified, including an individual participation rate of 22% and enrollment of younger, heavier, and more often female subjects when it was older men who tended to be more successful.

Implementation rate for the Standard of Care procedures that had been expected to support the intervention was 50%. Although there was no correlation evident between Standard of Care and weight outcomes, it suggested a lower Standard of Care than was intended for the lifestyle program to be successful. More hopeful for future planning efforts was the retention of subjects once enrolled: individual completion rate to six months was 81%, and 62% to one year. Participation of clinic teams and physicians was broad.

Reach. Fewer than half of our potentially eligible patients were solicited. Because lack of continuity is common in a teaching clinic, inconsistency in visit providers could have decreased the number of patients approached. Though its determination was a strength of the study, our penetration rate of 48% was lower than other real-world diabetes prevention programs. In a review of 38 such programs, only seven had reported their penetration, with five of the seven reported as "high" (> 66%).[6]

Even when offered the enrollment benefits of a free pair of athletic shoes and a free YMCA membership, more eligible patients declined than agreed to participate, suggesting that the simple elimination of certain cost barriers was not sufficient to achieve weight loss. This was consistent with a large survey of health and lifestyle practices of people at high risk of developing type 2 diabetes, where only 57% of those surveyed were even "considering" a plan to lose weight.[12] The higher rate of enrollment in acutely scheduled patients suggests a bias to offer the program preferentially to those thought most likely to enroll (though it says nothing about actual weight loss). Participation rates of other DPP-style studies must be interpreted carefully because denominators are not defined in the same way. In the Aziz review,[6] 92% of the 38 DPP-style studies reported participation rate and 71% had "low" (< 26%) participation. In this context, our participation rate of 44% was "moderate", higher than most of the studies reviewed.

Those who agree to the intervention are not necessarily reflective of the clinic population or typical of those who would benefit. Enrollment favored younger, heavier, and more often female patients. Women report attempting to lose weight 50% more often than men.[13] From prior experience with a childhood obesity study, our clinicians shared the common finding that they lack sensitivity to obesity at the lower end of the range.[14] This can be an issue because bariatric surgery is an alternative that may be more appropriate for heavier patients.

In terms of benefit, it was older men who tended to be more successful with weight loss efforts. Age increased success at meeting weight loss goals in the DPP study.[15] Likewise, Williamson[16] reported that, in the normal course of events, adults 55 and over tend to lose weight; among younger adults (and consistent with our study) women were more likely than men to gain weight.

Efficacy. Individual completion rates were good. The success of our subjects can be placed in the context of a population-based cohort study of adult family practice patients in the UK, which reported that the annual probability of an obese patient losing 5% of body weight was 1 in 5 to 1 in 12.[17] Weighted calculations based on sex and initial BMI category indicated that over the six-month interval of our study, the proportion of participants losing 5% of body weight was no more than experienced by the British patients in usual care.

Adoption. Referral to formal fitness programs outside the clinic can be costly for a low-income population and primary care physicians of challenged patients were eager for a no-cost program. The demand led to broad adoption of the program across residents and teams. Physician interest was consistent with a primary care survey in which 67% of providers indicated interest in being more involved in helping patients manage their weight. Notably, when providers' patients were surveyed, only 44% wanted their primary care physician to be more involved in helping them manage their weight.[18]

Implementation. Only 50% of Standard of Care procedures were completed, suggesting a weak base on which to build a lifestyle intervention. Lack of a relationship between Standard of Care score and successful weight loss suggests the possibility that a higher general adherence to standards of care is a prerequisite for weight loss. Differences across clinical campuses were observed and can inform nursing and process changes.

One barrier to completion of visits was the lack of funding for physician visits or laboratory assessments because uninsured patients who could not pay for these services may have declined them. Also, the scheduling system did not allow for the primary care physician to schedule follow-up visits more than one month out. The need for patients to make their own follow-up appointments in usual care introduced a selection bias. Many visits were for acute problems or involved multiple chronic conditions. Though all participants were at high risk of diabetes by virtue of their obesity, only a minority of visit notes mentioned weight loss, and many of these were generic comments and did not mention the lifestyle program. A survey of providers to assess barriers to weight management counseling suggested perceived futility based on how providers view their patients' ability to lose weight, as well as environmental factors beyond their control.[18]

Annual HbA1c had been deemed standard of care for patients with or at risk of diabetes who have made a commitment to lose weight and require focused visits to achieve that end. Most participants had no diagnosis that would drive obtaining routine lab values, and for those already diagnosed, the lack of a registry in the electronic medical record made population tracking problematic.

Evaluation of the implementation of this lifestyle intervention was limited by lack of feedback regarding why it was not offered to potentially eligible patients attending the clinic. When feedback was provided, it was often in the form of "patient not appropriate" without further description. One concern is that the reduction of obesity in this population

is impeded by their serious medical problems: about one quarter of our population is considered "permanently disabled". A related issue is that the reason for "permanent disability" is often not evident in the patient's medical chart, making its import hard to assess. Lack of consistency in providers can be a source of variability, and there was no assessment of how often a patient saw their regular provider at a usual care visit. Finally, the lack of efficacy of the intervention may have reduced provider and participant engagement and weakened measures of implementation.

In spite of the disappointing lack of efficacy of the intervention used in this study, valuable information was collected that can assist in planning future interventions in this setting. Physicians were eager to use a tool to help their obese, indigent patients. The rates of participant solicitation, enrollment, and retention were typical of other DPP-type studies. An electronic system supportive of scheduling and registry development was lacking during the intervention but has since been implemented. The most pressing need in the clinical setting may be to back-up provision of a simplified lifestyle intervention with greater engagement of providers at clinic visits. Alternatively, practitioners who wish to follow USPSTF recommendations to refer to intensive, multicomponent behavioral interventions may choose to consider evidence-based DPP adaptations such as the Group Organized – YMCA DPP,[5] which incorporates the DPP principles across a 16-lesson core curriculum phase, a 4-week training and refinement phase, and a long-term maintenance phase.

CONCLUSION

For an indigent population, overcoming cost barriers to gym membership, providing simple diet plans and a weekly support call was not sufficient to treat obesity effectively. For DPP adaptations to be tailored effectively for patients who experience a high burden of obesity and diabetes, researchers should provide detailed evaluation of program implementation.[19]

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Efficacy of a Lifestyle Program Designed to Help Indigent, Obese Adult Patients Lose Weight

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ABSTRACT

Introduction. Modest weight loss (5 to 7%) reduced the incidence of type II diabetes in the Diabetes Prevention Program (DDP) trial. A DPP-inspired lifestyle intervention requiring minimal patient self-data collection and tailored to low-SES patients through minimal cost was developed for our indigent, obese patients.

Methods. Obese (BMI ≥ 30 kg/m2), indigent (≤ 200% Federal Poverty Level) adults (age 18 - 70) were offered a no-cost weight loss intervention as an adjunct to their usual primary care in a residency outpatient clinic. The intervention provided options for diet plans and social support. The goal was to achieve a 5% loss of body weight over six months.

Results. The sample (n = 158) was 86% female and 62% white, with a median age of 45 and median BMI of 40.9. Two-thirds of subjects chose the 50% diet; YMCA membership was selected by all but one. The 5% weight loss goal was met by 12.8%; another 8.7% gained that amount. Subjects who either had pre-existing YMCA membership or used their provided membership were successful, relative to those who received but never used their membership (0.6% loss vs 0.9% gain; $p < 0.05$). Changes in weight over six months were observed in the youngest (gain of 3.9 lbs., $p < 0.05$) and the oldest (loss of 4.0 lbs., $p < 0.05$) age quartiles.

Conclusions. A DPP-inspired lifestyle intervention tailored to low-SES patients did not lead to overall weight loss, reinforcing that weight reduction programs must provide a significant amount of support for participants to see success. Older age and a behavioral commitment to physical activity improved the likelihood of success. ***KS J Med 2016;9(4):83-87.***

INTRODUCTION

Diabetes is a leading cause of morbidity and mortality worldwide.[1] In 2014, an estimated 422 million of the world's population lived with diabetes. The expectation is that by 2030, the number will increase to over 552 million. As of 2012, diabetes affected 29.1 million people in the US, with type II diabetes responsible for 90 - 95% of all cases.[2] Additionally, 86 million Americans have pre-diabetes with an increased risk for developing type II diabetes. The Diabetes Prevention Program (DDP) trial demonstrated that modest weight loss (5 to 7% of body weight) reduces the incidence of type II diabetes.[3] The United States Preventive Services Task Force (USPSTF) recommends screening all adults for obesity.[4] For patients with a body mass index (BMI) of 30 kg/m2 or higher, it is recommended that clinicians offer intensive, multicomponent behavioral interventions. Such interventions were used successfully by the DPP and were based on the three legs of nutrition, activity, and social support.

In our residency program outpatient clinic, many patients appropriate for referral to behavioral intervention are indigent, introducing an additional challenge. Financially and socially disadvantaged patients tend to suffer more from an inability to effect change because of social determinants of health.[5] Based on the principles of DPP, we developed and offered our indigent, obese patients a lifestyle intervention tailored to their economic circumstances through low cost, minimal record keeping options focused on a goal of restricting caloric intake and increasing caloric expenditure to reach weight loss of 5 to 7% over a six-month period.

METHODS

Participants. The program was designed by faculty of a large Family Medicine residency program to assist obese, indigent clinic patients with weight loss. Obese (BMI ≥ 30 kg/m2), indigent (≤ 200% Federal Poverty Level) adults (age 18 - 70) without contraindications to weight loss were included. Prospects were identified on daily reports of scheduled patients (based on age and most recent BMI); patients scheduled acutely were added occasionally to the list when identified by clinic staff. Patients were solicited at clinic visits by physicians or staff. Staff of the eight clinic teams referred interested patients to the study coordinator for additional screening and enrollment of eligible participants willing to provide informed consent. The protocol was approved by the Via Christi Institutional Review Board.

Lifestyle Program. Participants consented to a no-cost one year lifestyle intervention program, comprised of a six-month acute phase in which the goal was a 5% loss in body weight, followed by a six-month maintenance phase in which the goal was retention of weight loss. Physical activity was promoted by offering all participants a pedometer, a coupon for a pair of athletic shoes and socks, and their choice of either a membership to the YMCA or an exercise prescription. Nutrition was addressed by offering a choice of three simplified "diet plans". We believed choice was important to enhance participation or 'buy-in'. The first plan provided a specified calorie count, so participants did not need to count calories. The "meal plan" was centered on limiting calories to 900 to 1000 per day. The meal plan limited daily intake to two 11 oz. bottles of SlimFast©, one Healthy Choice© or Lean Cuisine© frozen meal, a piece of fruit, and another 100 calorie snack. The second option ("50% diet") reduced quantity without giving up favorite foods and was based on portion size and "simply eating half of whatever you have been eating".[6] A third plan displaced unhealthy eating with healthy habits. The final plan ("5210") is based on the 5210 plan used by Let's Go

Childhood Obesity Program (http://www.letsgo.org) and involves eating five fruits and vegetables per day, limiting "screen time" to two hours, engaging in one hour of physical activity, and having no sugared drinks or desserts in the house. Social support was in the form of a weekly call from a study coordinator, whose function was to provide a means of accountability, assistance in identifying barriers and solutions, and communication with the study investigators and clinic team. Weekly telephone support has been shown to be as successful as in-person support of intensive primary care weight loss interventions.[7] Availability to take the call, but no other structured information, was collected. Some funds were available to support subject transportation and child care needs as requested by the primary care physician or coordinator. The primary outcome was a six-month change in body weight; secondary outcomes included blood glucose/HgbA1c and maintenance of weight loss in the following six months.

Standard of Care. The lifestyle program was approved as research intended to operate against the clinic's self-defined Standard of Care "for patients with or at risk of diabetes who have made a commitment to lose weight and require focused visits to achieve that end". This Standard included visits to evaluate and counsel on the patient's progress scheduled at one month, three months, six months, nine months, and one year following initial evaluation, and measurement of HbA1c and lipid levels at baseline and one year. Weight, vital signs, and laboratory data were extracted from the patient's medical record, as were any visit notes pertinent to counseling on physical activity or nutrition.

Data Analysis. Descriptive statistics were used to characterize the population. Inferential statistics (analysis of variance, chi-square) compared groups statistically. Effect sizes (ES; Cohen's d, partial eta squared, Pearson correlation coefficient, or phi) estimated clinical significance. Analyses were conducted in SPSS and $p < 0.05$ (2-tail) was deemed statistically significant.

RESULTS

Participants. From a pool of 832 potential participants, study criteria excluded 89, leaving 743 patients potentially eligible (unless qualified by virtue of Medicaid insurance, indigency could not be assessed except through screening). We invited 356 and enrolled 158, thus capturing approximately 21% (158/743) of our population of interest. Of 158 participants enrolled, eight were excluded from analysis because they were or became ineligible and one was excluded because they had no visits and no data, leaving 149 participants in the Intent-to-Treat (ITT) sample.

Characteristics of the ITT subjects are shown in Table 1. The sample was largely female (85.9%) with a median age of 45.0 (IQR: 34.5 - 53.5) and median BMI of 40.9 (IQR: 35.9 - 46.1). About two-thirds were Caucasian and one-third were African-American. A minority (28%) had a diagnosis code of 250.xx (diabetes). Reflecting the indigent state of our patient population, Medicaid was the most common form of insurance (59%) and Medicare received prior to age 65 indicating disability was noted in over one-quarter of subjects.

Table 1. Characteristics of patients included in Intent-to-Treat sample (n = 149).[a]

		Median	IQR
Age		45.0	34.5 - 53.5
BMI		40.9	35.9 - 46.1
		n	%
Sex	Female	128	85.9
	Male	21	14.1
Race	White	92	61.7
	Black or African American	49	32.9
	Other	8	5.4
Diagnosis Code	250.xx	42	28.2
	No 250.xx	103	69.1
	Other	4	2.7
Insurance	Commercial	20	13.4
	Medicare only	12	8.1
	Unknown	16	10.7
	Medicaid	88	59.0
	Uninsured	13	8.7
Evidence of Disability[b]	Yes	40	26.8
	No	109	73.2
Source	Daily report	125	83.9
	Staff referral	24	16.1

[a]Numbers may not equal 100% due to rounding.
[b]Evidence of disability is Medicare insurance received before 65 years old.

Physical Activity. A single adult membership to the YMCA was selected as the physical activity option by 148 of 149 analysis subjects; only one subject, who was blind, chose "Exercise Prescription". Nine already had a membership (usually a family membership or employer-sponsored), and two others subsequently were unable to attend (one was prohibited by parole restrictions; one had an unpaid bill at the YMCA).

We paid for a single membership for 137 of the 149 subjects in the analysis population. Of the 137 subjects who accepted the YMCA membership and were presumed able to attend, 98 (72%) attended at least once. Subjects logged their attendance at the YMCA up to 21 times prior to the one-month visit, up to 44 times between one and three months, and up to 66 times between four and six months. Usage was generally not available for subjects who had their own membership.

Nutrition. Nutritional choice was missing from one participant, and one participant who began with the 5210 diet and immediately switched to the 50% diet was excluded from analysis. Most of the remainder (66%) initially chose the 50% diet plan; 23% chose meal replacement and 10% chose the 5210 plan. Subsequently, some subjects reported in their weekly support call that they had

changed their nutritional choice because of dissatisfaction with their initial choice, but this change was not tracked.

Social Support. Three coordinators were used during the study; two were physicians awaiting residency placement and the third was a research coordinator who conducted intervention programs in the community. Logs of support calls made by the coordinator were evaluated for the 138 subjects who attended more than the baseline visit. Seven (5%) were available for no more than a single call; 73 (49%) were available for fewer than half; and 58 (39%) were available for at least half.

Among the barriers to progress, participants most frequently noted medical problems (e.g., arthritis, recent surgery, back pain), transportation problems (e.g., no gas and car needing repairs), and family problems (e.g., death or illness in family). Five participants noted at some point during the study that they were homeless. Assistance with transportation (bus passes) was given to four subjects and child care (provided at the YMCA) was paid for three subjects.

Effectiveness. Average weight loss over six months was small (0.37 lb, ES = 0.0). Average loss was 0.5% of body weight at one month, 0.5% body weight at three months, and 0.2% at six months. When outcomes were classified against the goal of achieving 5% loss of body weight at six months, 19 (12.8%) were successful; 13 (8.7%) gained 5% of body weight, and 117 (78.5%) changed by less than 5% (Table 2).

Table 2. Weight outcomes overall, by sex, by age quartile (Intent-to-Treat sample, n = 149).

		n	%		
Overall Weight Loss					
6 month status	5% loss	19	12.8		
	< 5% change	117	78.5		
	5% gain	13	8.7		
		Mean	S.D.	Effect Size	p
Pounds lost at 6 months		0.4	11.1		
Subgroup Analyses[a]					
Pounds lost at 6 months by sex	Women, n = 127	-0.1	9.4		> .10
	Men, n = 21	2.7	18.4		> .10
Pounds lost at 6 months by age	18 - 34	-3.9	12.4	0.09	< .05
	35 - 45	0.7	10		> .10
	46 - 53	0.5	8.6		> .10
	54 - 65	4.0	11.9	0.10	< .05

[a]Repeated measures ANOVA.

The sexes did not differ in weight change. When examined within age quartiles, statistically significant changes in weight over six months were observed in the youngest (who gained 3.9 pounds, ES = 0.09, $p < 0.05$) and the oldest (who lost 4.0 pounds, ES = 0.10, $p < 0.05$) quartiles. Because attendance at the YMCA was unavailable for nine subjects who had a pre-existing membership, and zero for 39 subjects whose valid membership was paid by the investigators, we dichotomized attendance into those who had never used a study-provided membership and the remainder. Subjects who either had pre-existing YMCA membership or used a membership provided were successful, relative to those who received but never used their membership (0.6% loss vs 0.9% gain; $p < 0.05$; Table 3).

For the 107 who used or purchased a YMCA membership, about 20% were successful with weight loss, with no successes among the 39 who did not use their membership. There were no differences in percent weight loss at six months among the diet plans ($p = 0.44$). YMCA attendance increased with transportation or child care assistance, but weight loss did not necessarily increase.

Table 3. Weight outcomes overall, by sex, by age quartile (Intent-to-Treat sample, n = 149).

Source of membership	Subject	Study	Study
Use of membership	Unknown	Used	Not Used
n =	9	98	39
Weight loss (average %)	1.4	0.5	-0.9
Weight loss category			
Lost 5%	2 (22%)	17 (17%)	0 (0%)
Changed less than 5%	6 (67%)	72 (73%)	36 (92%)
Gained 5%	1 (11%)	9 (9%)	3 (8%)

Maintenance. The 121 completers at six months had consented to an additional six-month maintenance phase, but loss of funding led to early termination of 48. Only eight had a visit in the maintenance phase and their data were excluded. The remaining 73 subjects were included in the Intent-to-Continue analysis. The Individual Completion rate to one year in the maintenance phase was 62% (45 of 73).

The 45 completers to one year had average gains (vs baseline) of 0.4% body weight at six months, 1.0% body weight at nine months, and 0.1% at one year. When outcomes were classified as the proportion achieving 5% loss of body weight, five (11.1%) were successful at six months and 10 (22.2%) were successful at 12 months. Repeated measures analysis by sex did not reveal differences in weight across maintenance visits (Females: $p > .10$, ES = 0.01; Males: $p > 0.10$, ES = 0.11). Repeated measures analysis within age quartiles did not reveal differences in weight across maintenance visits (all p values > 0.10, ES < 0.06).

Secondary Outcomes. Laboratory values were examined to determine whether an initial (within the first month) value had been obtained for HbA1c, glucose, or lipids. Most subjects (93/149) had either HbA1c or glucose drawn by the one-month visit, but the quantity of missing data precluded inferential statistics.

DISCUSSION

The clinical goal of helping indigent, obese patients lose 5% of body weight in six months was not realized: 13% of the Intent-to-Treat population achieved this categorical goal, but 9% gained as much and average weight loss was only 0.2%. In those eligible for the maintenance segment, the additional six months doubled the odds of success. Success was associated with two additional factors. First, behavioral engagement (e.g., having a YMCA membership at study entry or using a study-provided membership at least once during the study) was evident in all who achieved the goal of 5% weight loss. Second, age quartile was associated positively with weight loss.

As in the DPP[3], we used a goal-based behavioral intervention, where all participants were given the same weight loss goal, but individualization was permitted in tailoring of intervention activities to the diverse population and those with low literacy. Our goal of 5% weight loss over six months was modestly lower than the 6% achieved in the DPP and associated with a 58% reduction in the incidence of diabetes. The intervention used by DPP[3] was simplified for application in our clinic. For physical activity, DPP offered supervised sessions and a goal of at least 150 min of moderate physical activities similar in intensity to brisk walking. In the current study, physical activity sessions were translated into YMCA membership. The YMCA is established as a user friendly and income considerate place for physical activity. They also provide trainers and other support staff within the basic membership fee. Monthly reports of sign-ins from the YMCA were a proxy for supervision of exercise. We added provision of athletic shoes to reduce barriers to physical activity further.

To address nutrition, DPP[3] participants were taught behavioral strategies to realize and maintain long-term changes in their fat and calorie intake. Our program relied on diet plans that required no calorie-counting and would be simple to understand for our population. We chose not to have intensive educational sessions based on our prior office experiences that these sessions would be attended poorly.[8] Alternatively, we opted for nutritional handouts and anticipated that physicians' instructions would fill in other educational deficiencies. Educational nutrition handouts were available from the research coordinator and/or the physician.

For social support in the DPP[3], each participant was assigned a "lifestyle coach" who made frequent contact with and motivated the participant. They also delivered a 16-session core curriculum that ensured all participants were taught the same basic information about nutrition, physical activity, and behavioral self-management. In our program, support personnel called the patients on a weekly basis, both on the assumption that accountability is a major factor for success and a reduction in overall patient expense that would be required for similarly frequent office encounters. This meant limiting participants to only those who were English-speaking. The primary goal was to make contact with the patient, provide accountability, and resolve potential obstructions to success. Based on resources, we designated the frequency of patient contact to be weekly, documenting actual contacts and attempts to contact each patient. Contact was difficult in a population that was not able consistently to afford phone access. DPP provided funds for implementing strategies to overcome barriers in individual patients. Our program also had funds to pay for transportation, child care, or other amenities. The anticipated solution of providing bus passes was impeded when some subjects needed car repairs or gas instead, which were not covered.

Limitations included those associated with effectiveness studies, such as lack of blinding, lack of a control group, and flexibility in intervention choice. There was no measure of adherence to the diet choices or uptake of the nutritional intervention. This limitation was felt more keenly given the link between success in weight loss and adherence to the activity intervention. Verifying baseline intake for the patient would have given more objective and comparative data to support weight loss efforts. The intervention was not as intensive as the DPP. A more rigorous program might have resulted in more weight loss.

CONCLUSION

A DPP-based lifestyle intervention tailored to low-SES patients through low cost, minimal record keeping options did not lead to the hypothesized loss of 5% body weight in this sample of patients. Factors associated with weight loss success included age quartile and a behavioral commitment to physical activity. Together, these factors suggested that patient commitment must be high and that the support provided by the program must be intensive and individual. Future research should consider evaluation of patient readiness combined with simplicity and individual, intensive accountability and support.

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Second Generation Patient Specific Total Knees Demonstrate a Higher Manipulation Rate Compared with "Off-the-shelf" Implants

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ABSTRACT

Introduction. Patient specific total knee arthroplasty (TKA) theoretically provides a more accurate fit to the native knee but may have difficulty achieving full range of motion (ROM) post-operatively. Post-operative ROM data were compared between patients who underwent cemented patient-specific cruciate-retaining (PSCR) and standard cemented posterior-stabilized (SPS) TKAs.

Methods. PSCR and SPS TKAs that were performed from January 2014 to September 2015 by the same surgeon using the same post-operative protocols at two selected facilities were reviewed. Two- and six-week post-operative ROM data were obtained and the number of patients with knee flexion less than 110° was recorded.

Results. Twenty-one patients in the PSCR group and 57 patients in the SPS group were included. The percentage of patients with knee flexion less than 110° was similar in both groups pre-operatively (10% vs 14%, p = 0.60) and two-week post-operatively (57% vs 68%, p = 0.35). However, at six-week post-operatively there was significant difference (29% vs 7%, p = 0.01).

Conclusions. These results provide evidence to alert orthopaedic surgeons when using these patient specific implants versus conventional TKA methods. Patients whose TKA was performed using patient specific cutting guides struggled to obtain 110° of knee flexion. Close monitoring, aggressive physical therapy, and early manipulation are recommended when using patient specific cutting guides and custom total knee implants. Further evaluation in a larger group of patients is warranted. ***KS J Med 2016;9(4):88-92.***

INTRODUCTION

Total knee arthroplasty (TKA) is a successful surgical intervention for addressing pain and improving patient function. It is one of the most common orthopaedic procedures performed and whose demand continues to increase.[1-4] With the increasing demand comes a focus on ways to achieve a superior outcome. Poor alignment is a well-known risk factor for implant failure[5-23] which has led to improvements in surgical technique, instrumentation, and implant design.[24,25] One innovation is the use of patient-specific or custom cutting-blocks and custom implants, which theoretically provide a more accurate fit to the contour of the native knee,[20,26-30] thus allowing for a superior functional outcome and more efficient use of intraoperative resources.

Patient specific total knee replacements have been designed using computer technology utilizing preoperative magnetic resonance imaging (MRI) or computed topography (CT) to construct a three-dimensional representation of the knee. These data are used to create single-use patient-specific cutting-blocks for both the femur and tibia, which results in more accurate bone cuts for acceptable mechanical alignment and soft tissue balancing without the intra-operative reliance on fixed anatomical landmarks that often are distorted secondary to chronic arthritic changes (i.e., osteophytes). Additionally, these systems allow either predetermination of implant sizes or customized implants for each patient for both the femur and tibia prior to the operation.

Several studies compared these patient-specific instrumentations with standard instrumentation in terms of cost-effectiveness, coronal alignment, and operation time.[4,22,23,31-50] To our knowledge, however, the outcomes of these implants have not been as well studied.[4,37,39] We, therefore, retrospectively reviewed consecutive patients undergoing cemented patient-specific cruciate-retaining (PSCR) TKA and compared those patients to those who received a standard cemented posterior-stabilized (SPS) TKA, focusing on rates of postoperative knee manipulation under anesthesia (MUA). At the time of the study, a posterior stabilized custom knee replacement was not available on the market.

PATIENTS AND METHODS

Institutional review board approval was obtained for the study. A retrospective chart review was performed looking at consecutive PSCR TKAs from January 2014 through September 2015 utilizing the ConforMIS I-Total G2 TKA system (ConforMIS, Inc, Bedford, MA; PSCR group). Patients who underwent SPS TKA during that same time period by the same surgeon were selected, based on the inclusion criteria, to serve as a control group, and the number of patients for this group was selected 3.5 times more than the PSCR group to reduce the percentage of outliers and, therefore, obtain better statistical analysis. In this SPS group, the implant was either Stelkast (Proven Gen-Flex, McMurray, PA) or Zimmer Gender Solutions NexGen (Zimmer, Inc., Warsaw, IN), ATTUNE (DePuy Synthes, Warsaw, IN), or Donjoy Motivation PS (Vista, CA). These two groups (PSCR and SPS groups) were operated on at two surgical centers.

Subject Selection. Inclusion criteria were PSCR TKAs and SPS TKAs performed from January 2014 through September 2015 by the lead surgeon at the two selected facilities. Patients selected were those with the principal diagnosis of osteoarthritis who underwent primary TKA. Patients with a history of trauma and/or a history of surgery on the operative knee also were included as long as there was no form of retained hardware. Since the production of the patient specific cutting guides was dependent on the quality of the preoperative CT, it was determined that the presence of hardware may interfere with the

generation of accurate guides. SPS TKA patients were selected based on similar age, side, deformity, diagnosis, and preoperative range of motion with patients who underwent PSCR TKAs.

Exclusion criteria included all patients who underwent PSCR or SPS TKAs outside of January 2014 through September 2015 and not by the lead surgeon at the two selected facilities. Patients were excluded from the study if they underwent the pre-operative planning but the patient specific cutting guides were not utilized during the procedure.

Patient-Specific TKA Surgical Technique. Pre-operative planning was performed as described by the manufacturer's protocol. Prior to surgery, each patient had CT images of the operative lower extremity from hip to ankle performed. The CT imaging data were provided to the manufacturer who was responsible for the custom fabrication of the femoral and tibial patient specific cutting guides and custom total knee implants. Scheduling of the operation was made once the patient specific cutting guides and implants were provided by the manufacturer. This pre-operative planning usually required at least seven weeks from the time of the initial visit.

The surgery was performed through a traditional medial parapatellar approach under tourniquet control. For the PSCR TKA, the posterior cruciate ligament (PCL) was left intact, whereas for the SPS TKA the PCL was resected. Once bony exposures were achieved, and prior to any revision or resection of bone, the patient specific cutting guides were placed as manufacturer guidelines directed. The guides were pinned after appropriate placement. These initial steps were performed in similar fashion for both the femur and the tibia. In each of the operations, the femur was addressed first. After standard cuts were made, the trial femoral implant was placed and the surgeon evaluated femoral component size, femoral anterior-posterior translation, femoral component rotation, and femoral proximal-distal translation.

A similar procedure was performed on the tibia including placement of patient specific cutting guide and standard cuts. Following completion of the initial bone cuts, the tibial trial component was placed. Component placement was evaluated for appropriate tibial component size, tibial slope, tibial rotation, and tibial proximal-distal translation.

Manipulation under Anesthesia (MUA) Technique. Subjects who had knee flexion less than 110° by six-week post-operative were selected for MUA. A previous study indicated that patients with knee flexion less than 110° were not able to kneel,[51] and kneeling is one of the important functions of the knee joint required for many activities of daily living and in certain occupations.[52,53] Therefore, this study defined knee flexion less than 110° as the criterion for MUA. The procedure was performed with the patient taken to the operating room where general anesthesia was induced. After adequate muscle relaxation was achieved, the ipsilateral hip was flexed to 90°. To minimize the risk of iatrogenic fracture, the surgeons' hands were placed on the distal femur and proximal tibia close to the knee joint line. Steady progressive loading was applied to the tibia to flex the knee until audible and palpable break of adhesions were felt. The final range of motion (ROM) then was recorded. Patients underwent aggressive physical therapy in the post-operative period.

Data Collection. A chart review was performed of the pre-operative assessment and included documentation of gender, age, height, weight, body mass index (BMI), side of the knee, and deformities in the knee. Pre-operative ROM also was obtained from the history and physical. All patients underwent the same post-operative protocol, including post-operative physical therapy. Post-operative ROM was obtained at two- and six-weeks after surgery. All post-operative measurements were taken by a physical therapist with the aid of a goniometer to ensure accurate measurements. If the patient underwent a subsequent MUA, it was recorded along with post-MUA ROM. Two- and six-week post-operative ROM data were reviewed and the number of patients with knee flexion less than 110° was recorded.

STATISTICAL ANALYSIS

The chi-square test using SPSS software (Version 19.0; SPSS Inc, Chicago, IL) was used to determine if there were any observed differences between the PSCR and SPS TKAs with respect to knee flexion pre-operatively and at two- and six-week post-operatively. The level of significant difference was defined as $p < 0.05$.

RESULTS

There were a total of 96 patients that met the inclusion criteria, 22 patients (28%) in the PSCR group and 74 patients (72%) in the SPS group. One of the 22 patients in the PSCR group was excluded due to a popliteal artery thrombosis that subsequently led to above knee amputation in the immediate post-operative period. Seventeen (23%) out of the 74 patients in the SPS group were excluded due to lack of follow-up information, resulting in a total of 57 patients for the SPS group.

Table 1 summarizes the demographic profile of the patients for this study. Of the 21 patients in the PSCR group, 14 were females (67%) and 7 were males (33%). In the 57 patients in the SPS group, 41 were females (72%) and 16 were males (28%). The mean age for PSCR and SPS groups were 59 ± 10 years (range: 36 - 72 years) and 65 ± 10 years (range: 47 - 89 years), respectively. The mean BMI for PSCR group was 30.7 ± 6.7 kg/m2 (range: 21.6 - 46.8 kg/m2), and 35.0 ± 7.0 kg/m2 (range: 23.0 - 51.6 kg/m2) for the SPS group.

The summary of patients with knee flexion less than 110° is shown in Table 2. The SPS group had a higher percentage of patients with knee flexion less than 110° pre-operatively (14%) compared to the PSCR group (10%). Statistically, there was no difference between these two groups ($p = 0.60$). At the two-week post-operative visit, this trend continued with 68% of 57 patients in the SPS group versus 12 (57%) of 21 patients in the PSCR group ($p = 0.35$). However, at the six-week post-operative period, this trend significantly changed with 4 (7%) out of 57 patients in the SPS group having less than 110° of knee flexion compared

with 6 (29%) out of 21 patients in the PSCR group (p = 0.01). The SPS group went from 68% of patients with less than 110° of flexion to only 7% during the two- to six-week post-operative time course. In comparison, the PSCR group went from 57% to 29%.

Table 1. Patient demographics.

		PSCR Group (N = 21)	SPS Group (N = 57)
Gender	Female	14 (67%)	41 (72%)
	Male	7 (33%)	16 (28%)
Age (years, mean ± SD) (range)		59 ± 10 (36 - 72)	65 ± 10 (47 - 89)
BMI (kg/m^2, mean ± SD) (range)		30.7 ± 6.7 (21.6 - 46.8)	35.0 ± 7.0 (23.0 - 51.6)
Height (inches, mean ± SD) (range)		67 ± 4 (61 - 75)	66 ± 4 (56 - 74)
Weight (lbs., mean ± SD) (range)		196 ± 53 (126 - 319)	216 ± 51 (133 - 337)
Side	Left	7 (33%)	26 (46%)
	Right	14 (67%)	31 (54%)

Table 2. Patients with knee flexion less than 110°.

	PSCR Group (N = 21)	SPS Group (N = 57)	p value
Pre-operative	2 (10%)	8 (14%)	0.60
2-week post-operative	12 (57%)	39 (68%)	0.35
6-week post-operative	6 (29%)	4 (7%)	0.01

All six patients in the PSCR group who had less than 110° of flexion six-week post-operatively underwent a MUA. Five significantly improved (average: 24 degrees, range: 10 - 40 degrees) their knee flexion to at least 115°. The other ultimately underwent a second MUA.

Only one of the four patients in the SPS group with less than 110° of flexion six-week post-operatively underwent a MUA. The patient improved knee flexion from 95 to 110°. One patient had a post-operative stroke severely affecting the operative extremity in the immediate post-operative period. This patient ended up with 90° of flexion but did not have a MUA secondary to lack of motor function in the operative extremity. The other two patients presented with knee flexion of 105° at six-week post-operatively; both patients were counseled but elected not to undergo a MUA and improved ROM with further therapy. They had no functional limitations at that time.

DISCUSSION

Patients whoseTKAs were performed using cruciate retaining patient specific implants with custom cutting guides struggle to obtain knee flexion of 110°, which potentially could restrict patients from kneeling. Caution should be taken when using patient specific cutting guides and custom total knee implants. Patient specific or custom implants have the theoretical advantage of providing a more accurate fit to the contour of the native knee which is hoped will allow for a superior functional outcome, but they were not a substitute for careful preoperative planning, good clinical and intraoperative judgment, appropriate soft tissue balancing, and precise implantation technique.

Bali and colleagues[33] prospectively studied 32 TKAs performed in 29 patients with MRI-based custom cutting guides. Their results showed that 29 of the 32 knees had a mechanical axis restored to within 3° of neutral, and they concluded that this technology can be used safely in most cases of osteoarthritis of the knee. However, they did not study the functional outcome of these patients. In our study, the rate of knee flexion less than 110° in the PSCR group was significantly higher compared with the SPS group. There is no clear evidence for this lack of knee flexion in the PSCR group. It is suspected that the close fit of the implants may place the patient at risk for stiffness. There also could be errors in the data input or in the manufacturing of the cutting-blocks and implants which could lead to difficulty with ROM. Another possibility for the lack of post-operative knee flexion may be the over reliance on the custom design and lack of attention to proper soft tissue balancing. The patient specific cutting guides and implants produce accurate and precise limb alignment.[22] Static alignment is unfortunately only one variable that can affect TKA performance. One of the major disadvantages of using the custom guides and implants is that no other instrument can be used intra-operatively to judge proper bony cuts and soft tissues balancing.[22]

There are several limitations of this study. First, this was a retrospective chart review utilizing information that had to have been documented accurately in the medical record. Second, this study had a small sample size for the PSCR group, which prevents applying tests of significance due to a low power. The low number of procedures performed in the PSCR group was unavoidable because the treating surgeon stopped using the implant secondary to concerns over stiffness as the overall functional outcomes were found not to be satisfactory as the study progressed. This study compared cruciate retaining (CR) TKAs to the posterior stabilized (PS) TKAs. These designs are based on the retention or sacrifice of the posterior cruciate ligament. Several other cohort studies and randomized controlled trial studies have shown no difference in flexion or range of motion between the two designs.[54-64] Given the available research models, we feel that the data are valid for the current investigation. One other weakness of the present study is the ROM measurements were taken by different therapists at different places. Nevertheless, this study contributes to the available literature on the functional outcomes of knee flexion for patient-specific total knee replacements. Further evaluation in a larger group of patients is required to resolve the question of functional results for the patient specific CR TKA.

CONCLUSION

The findings of this study provide additional evidence on the functional outcomes when using patient specific cutting guides/implants in TKA. Close monitoring, aggressive physical therapy, and early manipulation is recommended when using patient specific cutting guides and custom total knee implants.

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Early Outcomes of Cemented versus Cementless Total Knee Arthroplasty

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ABSTRACT

Introduction. Total knee arthroplasty (TKA) has been proven to be very effective for long-term pain relief in the degenerative knee. Few studies have investigated short-term clinical and functional outcomes between the cemented and cementless TKA. The specific aim of this study was to assess the potential difference of functional outcomes in the early post-operative period between these two surgical options using the Knee Society Score (KSS) and range of motion (ROM).

Methods. A total of 164 knees that had undergone TKA by a single surgeon at a single institution between 2007 and 2010 were reviewed. Three different TKA prosthetic designs (cruciate retaining (CR), posterior stabilized (PS) and cruciate substituting (CS)) were included. Data collection included patient demographics, pre- and post-operative ROM, and pre- and post-operative KSS at each visit (1.5 months, 3 months, and 12 months). Two separate KSS scores were assigned: functional score and clinical score.

Results. Sixty-seven knees underwent cemented TKA and 97 knees underwent cementless TKA. No significant difference was recognized in either age or body mass index for these two TKA groups. The cementless group showed a significant early ROM improvement after 1.5 months post-operative ($p < 0.05$), while the cemented group showed ROM improvement only after three months post-operative. No significant difference was detected in terms of KSS between the cemented and cementless TKA groups at each measured time period. Both groups showed marked KSS improvement (cemented: 135%, cementless: 125%) after 1.5 months post-operative and the KSS seemed to be stabilized after three months post-operative for both groups (cemented: $p = 0.36$; cementless: $p = 0.07$).

Conclusions. There was a significant early ROM improvement for the cementless TKA group compared to the cemented TKA group, but no statistical significant difference was noted in KSS in the early post-operative period when comparing cemented and cementless TKA groups. The findings provide evidence that cementless TKA patients can undergo an identical post-operative protocol to cemented TKA, without concerns about implant stability or function. ***KS J Med 2016;9(4):93-98.***

INTRODUCTION

The field of orthopedic surgery constantly is searching for more effective and efficient ways to provide patients with the most high quality care. Total knee arthroplasty (TKA) is the standard of care in treatment of end-stage degenerative joint disease of the knee. TKA generally results in relief of pain, improvement of physical function, and a very high level of patient satisfaction.[1,2] As the demand for TKA increases and the procedure is performed more often in younger (fifty-five years or less) and more active patients,[3-8] both long-term clinical outcome and survival rates need to be considered. Early postoperative physical therapy, pain control, and postoperative motion are also important aspects of patient care that must be addressed.

Traditional cemented TKA has demonstrated good clinical outcomes and high survivorship in the general osteoarthritis population. Cemented TKA also has shown a low rate of aseptic loosening in long-term studies.[9-13] However, osteolysis at the cement-bone interface has been demonstrated and raises the question about the long-term durability of cemented TKA.[2,14,15] Cementless TKAs have been developed in an attempt to improve the longevity of implants. An implant that allows bony ingrowth at the bone-implant interface theoretically increases the stability of the implant by creating a biologic fixation that has the ability to remodel over time.[3-5,16-21]

Although several studies have compared intermediate and long-term results of survivability and patient outcome scores for the cemented and cementless TKA,[2,12,14,15,17-27] to our knowledge there are no current studies that investigate short-term clinical and functional results between these two surgical options. With some data suggesting that cementless implants may offer more long-term stability, it is important also to assess the early post-operative outcomes of cementless TKA. Early physical therapy, pain control, range of motion, and post-operative activity are important to patient outcomes and satisfaction. It is important to determine if those cementless TKA patients can undergo an identical post-operative protocol to cemented TKA, without concerns about implant stability or function. The specific aim of this study was to assess the potential difference of functional outcomes in the early post-operative period between cemented and cementless TKA using the Knee Society Score (KSS) and range of motion (ROM).

MATERIALS AND METHODS

A retrospective study was performed on a total of 164 knees. TKAs were performed by or under the direct supervision of the senior author, at a single institution, between 2007 and 2010. These patients were treated with either cemented or cementless Stryker Duracon TKA prostheses (Stryker Orthopaedics, Mahwah, NJ) based on the primary surgeon's clinical judgment and shared decision making with the patient. Before commencing, this study protocol was reviewed and approved by Institutional Review Board.

Patients between 35 and 80 years of age that received TKA with either cemented TKA prosthesis or press-fit cementless prosthesis were included regardless of age, gender, body mass index (BMI), bone density, medical comorbidities, or social factors. Patients that did not undergo total knee arthroplasty with either prosthesis, and patients who had undergone previous knee replacement surgery, were excluded.

Three different TKA prosthetic designs with identical external geometries and dimensions were included in this study: cruciate retaining (CR), posterior stabilized (PS) and cruciate substituting (CS). The cementless components have a porous press-fit surface with hydroxyapatite coating for contact with the bone cut surfaces, whereas the cemented components have a smooth non-porous finish. Standard tibial polyethylene inserts were used.

Standard TKA surgical techniques were performed on each patient, and a tourniquet was used. The knee was approached through a midline incision with a standard medial parapatellar arthrotomy. Bone cuts were made using the manufacturer's protocol and cutting blocks. A decision was made regarding posterior cruciate retaining or sparing technique based on intra-operative stability as determined by the primary surgeon. In knees with cemented fixation, the cut surfaces of both femur and tibia were washed with normal saline solution by pulsatile lavage to remove blood, fat, bone marrow, and other bone debris. The femoral and tibial implant components were implanted using the Surgical Simplex-P bone cement (Stryker Howmedica Osteonics, Mahwah, NJ). For tibial implant, the positive pressure intrusion technique was performed by applying bone cement onto the tibial bone cut surface, then finger packing the cement into the bone. The tibial component was impacted into place. For femoral implant, cement was applied to the anterior chamfer and flange of the femur, and also applied to the distal and posterior chamfer regions of the femoral component. Excess cement was removed from around the implants, and the knee was held in full extension until the cement had polymerized completely. In knees with cementless fixation, femoral and tibial components were inserted with a press fit directly onto the cut bony surfaces. Component stability was confirmed manually by flexing and extending the knee to extremes of motion, and applying varus and valgus stress.

Data collection included patient demographics, pre- and post-operative range of motion (ROM), and knee society scores[28] at each visit. Patient demographic data included patient age, sex, weight, height, body mass index (BMI), and primary diagnosis. The active ROM of the knee with the patient in the supine position was determined pre-operatively and at three follow-up visits (1.5 months, 3 months, and 12 months) using a standard goniometer. Knee scores were calculated with the system established by the Knee Society.[28] Two separate scores were assigned: functional and clinical scores. The functional score was based on the patient's ability to walk, climb stairs, and use walking aids; whereas the clinical score was related to patient pain, range of motion, and stability. All patients with either cemented or cementless TKA received the same supervised post-operative care including: early mobilization (out of bed the day after surgery), weight bearing as tolerated, and, for most, formal physical therapy.

STATISTICAL ANALYSIS

Independent samples t-tests using SPSS software (Version 19.0; SPSS Inc, Chicago, IL) with 95% confidence interval were used to determine significant differences in numerical variables (age, BMI, ROM, and KSS) between the cemented TKA prosthesis and the press-fit cementless prosthesis.

RESULTS

A total of 164 consecutive knees (139 patients) revealed that 67 knees (59 patients) were in the cemented TKA group and 97 knees (80 patients) were in the cementless TKA group. Out of the 67 knees in the cemented TKA group, 37 knees were female and 30 were male, while out of the 97 knees in the cementless TKA group, 51 were female and 46 were male. The mean patient ages were 55.7 ± 6.1 years (range: 36 - 65) for the cemented TKA group and 57.3 ± 8.8 years (range: 37 - 79) for the cementless TKA group. The mean patient BMI was 36 ± 8 (range: 22 - 55) for the cemented TKA group and 35 ± 8 (range: 20 - 59) for the cementless TKA group. No significant difference was recognized in either age or BMI between these two groups (Table 1).

Table 1. Details of patient demographic data for cemented and cementless TKA prosthesis design.

	Implant design	Number of knees	Age		Female	Male	BMI	
			Mean ± SD (range)	p value			Mean ± SD (range)	p value
Cemented	PS	8 (12%)	54.3 ± 6.9 (43 - 61)	0.20	5	3	33 ± 5 (24 - 38)	0.37
	CR	44 (66%)	55.8 ± 5.9 (36 - 65)		24	20	36 ± 8 (25 - 52)	
	CS	15 (22%)	56.3 ± 6.4 (44 - 63)		8	7	37 ± 10 (22-55)	
Cementless	PS	7 (7%)	50.6 ± 4.5 (44 - 54)		3	4	36 ± 7 (25 - 42)	
	CR	27 (28%)	57.3 ± 8.5 (43 - 79)		12	15	32 ± 8 (22 - 53)	
	CS	63 (65%)	58.1 ± 9.0 (37 - 79)		36	27	36 ± 8 (20 - 59)	

RANGE OF MOTION (ROM)

When the pre- and post-operative ROM for both groups were compared, the cementless group showed a significant early improvement at the 1.5-month post-operative time (cemented: 3º improvement; cementless: 4º improvement), while the cemented group showed improvement only at the 3-month post-operative point (cemented: 10º improvement; cementless: 9º improvement; Figure 1, p = 0.42). For both cemented and cementless TKA groups, the ROM seemed to be stabilized at the 3-month post-operative time,

as there were no significant differences detected between the 3-month and 12-month period (Table 2). However, there was a trend of improvement in ROM from pre-operative to 12-month post-operative for both groups (Figure 1, Table 2).

When the ROM was compared between each time period and on each individual TKA prosthetic design, the PS TKA prosthetic design had no significant difference apparent for both cemented and cementless TKA group (Table 3), but this could be due to low power (cemented: n = 8; cementless: n = 7). For the CR TKA prosthetic design, the CR-cementless group showed a significant early improvement at the 1.5-month post-operative point ($p < 0.05$, Figure 2a; Table 3), while the CR-cemented group showed improvement only at the 3-month post-operative time, and there were no statistically significant differences in ROM between Pre-Op and the 1.5-month period for the cemented TKA group (Figure 2b, Table 3). For the CS TKA prosthetic design, the CS-cemented group showed a slow improvement in terms of ROM from pre- to post-operative with no significant differences detected between each time period; whereas the CS-cementless group exhibited a significant improvement in ROM after three months post-operative (Figure 2, Table 3).

Table 2. Statistical analyses for range of motion.

			p value
Cemented	Pre-Op	1.5 months	0.419
		3 months	0.000
		12 months	0.000
	1.5 months	3 months	0.012
		12 months	0.000
	3 months	12 months	0.067
Cementless	Pre-Op	1.5 months	0.006
		3 months	0.000
		12 months	0.000
	1.5 months	3 months	0.001
		12 months	0.000
	3 months	12 months	0.378
Pre-Op	Cemented	Cementless	0.210
1.5 months	Cemented	Cementless	0.014
3 months	Cemented	Cementless	0.075
12 months	Cemented	Cementless	0.546

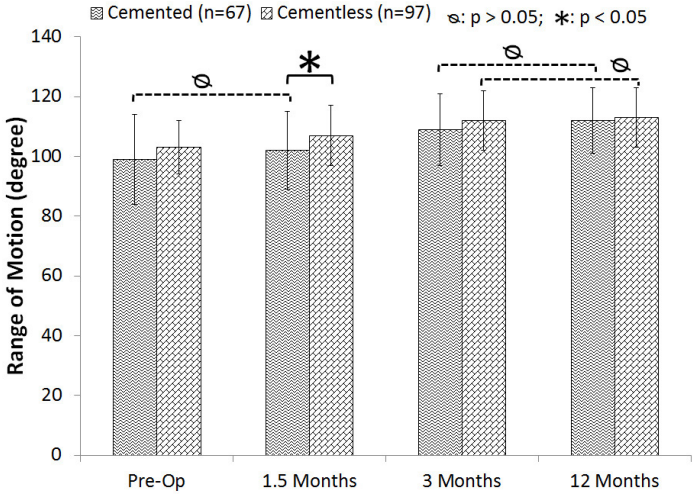

Figure 1. Range of motion results.

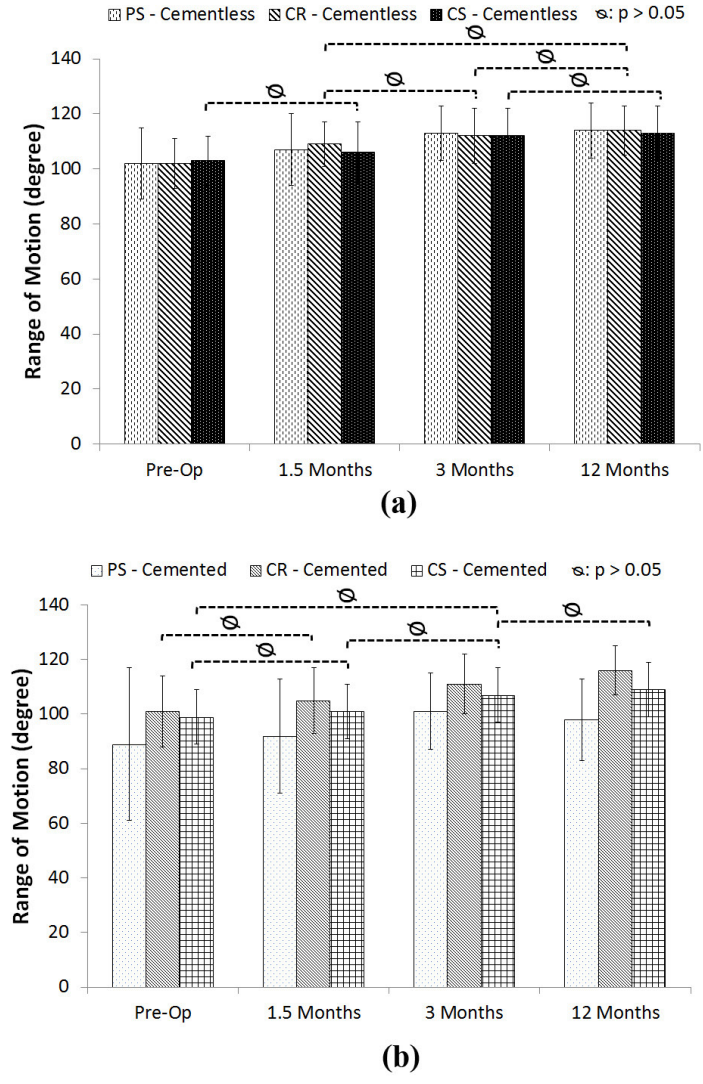

Figure 2. Range of motion of individual implant design: (a) cementless TKA and (b) cemented TKA.

Table 3. Statistical analyses for ROM for the three different TKA prosthetic designs.

				p value
PS TKA	Cemented (n = 8)	Pre-Op	1.5 months	0.93
			3 months	0.42
			12 months	0.48
		1.5 months	3 months	0.35
			12 months	0.44
		3 months	12 months	0.91
	Cementless (n = 7)	Pre-Op	1.5 months	0.68
			3 months	0.27
			12 months	0.24
		1.5 months	3 months	0.47
			12 months	0.41
		3 months	12 months	0.90
CR TKA	Cemented (n = 44)	Pre-Op	1.5 months	0.33
			3 months	0.00
			12 months	0.00
		1.5 months	3 months	0.01
			12 months	0.00
		3 months	12 months	0.03
	Cementless (n = 27)	Pre-Op	1.5 months	0.00
			3 months	0.00
			12 months	0.00
		1.5 months	3 months	0.23
			12 months	0.05
		3 months	12 months	0.50
CS TKA	Cemented (n = 15)	Pre-Op	1.5 months	0.95
			3 months	0.10
			12 months	0.03
		1.5 months	3 months	0.08
			12 months	0.02
		3 months	12 months	0.49
	Cementless (n = 63)	Pre-Op	1.5 months	0.18
			3 months	0.00
			12 months	0.00
		1.5 months	3 months	0.00
			12 months	0.00
		3 months	12 months	0.55

KNEE SOCIETY SCORE (KSS)

Using the KSS outcome score, no significant differences were detected between the cemented and cementless TKA groups at each measured time period (Figure 3). Both groups showed a significant improvement (cemented: 135%, cementless: 125%) in KSS at 1.5 months post-operative and appeared to be stabilized after three months, with no statistically significant differences detected between the 3-month and 12-month post-operative periods (Figure 3).

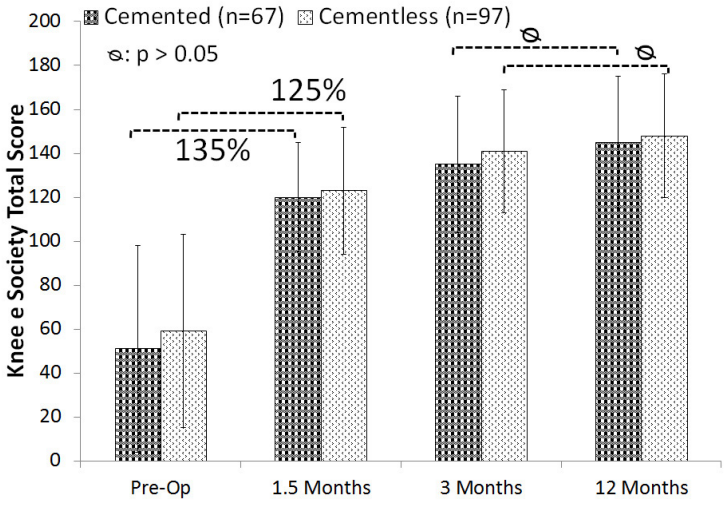

Figure 3. Knee Society Score results.

The Knee Society Clinical Score was compared between each time period and on each individual TKA prosthetic design. The PS TKA prosthetic design had no significant clinical improvement for the cementless TKA group between each measured time period, but this could be due to low power (n = 7). However, there was a significant clinical improvement detected between the cemented TKA group when comparing the pre-operative and the 1.5-month post-operative period (Figure 4a). For the CR TKA prosthetic design, both the CR-cemented and the CR-cementless groups showed a significant clinical improvement at the 1.5-month post-operative point and continued to show improvement at the 3-month post-operative time ($p < 0.05$, Figure 4a). For the CS TKA prosthetic design (which is similar to the CR TKA) both the CS-cemented and the CS-cementless groups showed a significant clinical improvement at the 1.5-month post-operative point and continued to show improvement after three months ($p < 0.05$, Figure 4a).

When the Knee Society Functional Score was compared between each time period and on each individual TKA prosthetic design, the PS-cemented TKA prosthetic design showed a significant functional improvement between the pre-operative and the 1.5-month post-operative periods (Figure 4b). The CR-cemented group also showed no significant functional improvement between each measured time period. However, the CR-cementless TKA group showed a significant functional improvement at the 1.5-month post-operative point ($p < 0.05$, Figure 4b), but there was no significant

improvement beyond the 3-month post-operative interval. For the CS TKA prosthetic design, both the CS-cemented and the CS-cementless groups showed a significant functional improvement at the 1.5-month post-operative time and continued to show improvement at 3-month post-operative ($p < 0.05$). However, the knee functional score appeared to be stabilized after three months post-operative for both groups, with no statistically significant difference detected between 3-month and 12-month post-operative period (Figure 4b).

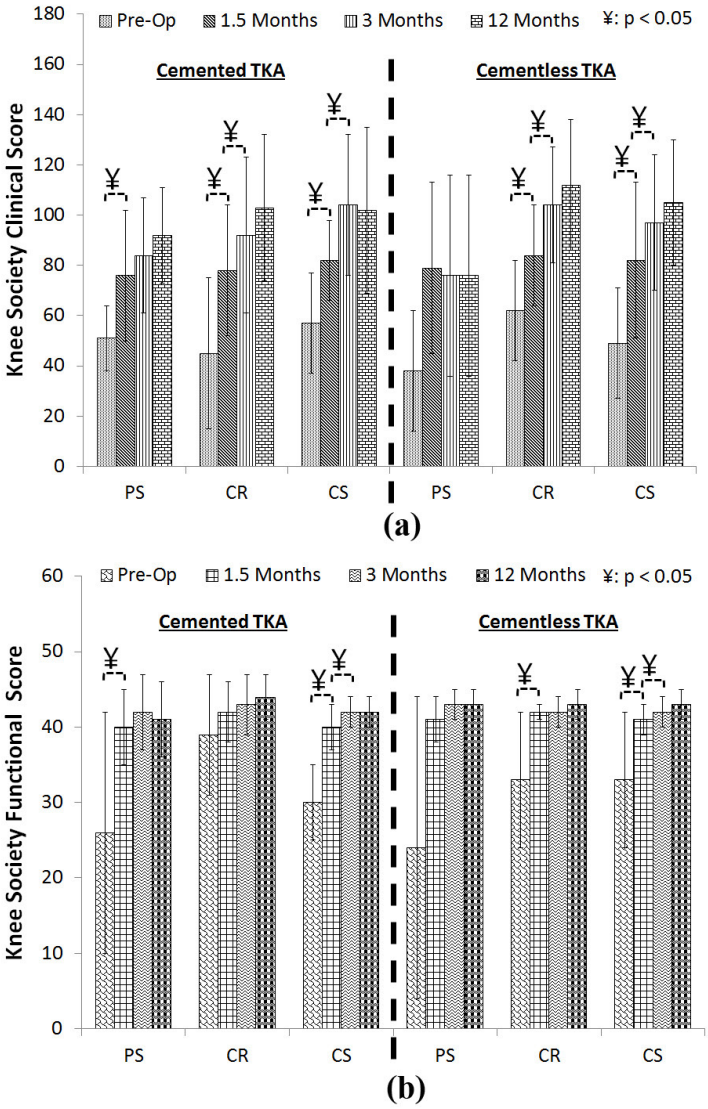

Figure 4. Knee Society Scores of individual implant design: (a) Knee Society Clinical Score and (b) Knee Society Functional Score.

DISCUSSION

The success of modern TKA has come as a result of the evolution of implant design, improved surgical techniques, careful patient selection, and standardized post-operative rehabilitation protocols.[24,29-31] Laboratory and clinical studies have shown that bony ingrowth into porous hydroxyapatite-coated implants can provide a stable interface for component fixation.[32] Hydroxyapatite has been shown to convert a movement-induced fibrous membrane into a bony implant anchor.[33] However, bone ingrowth needs time, and restriction of post-operative knee motion and limitation of weight bearing is not conducive to successful outcomes and patient satisfaction.[34] The greatest improvement in knee flexion occurs within the first six to seven weeks post-operatively. TKA patients that acquire 95 - 120° of knee flexion at 12-months post-operative achieve satisfactory function and perform most activities of daily living.[34-37]

These studies highlight the importance of early active knee flexion for maximum patient satisfaction, and the findings of our study are congruent with these studies. The cementless TKA group showed a significant early improvement ROM compared to the cemented TKA group.

Some potential benefits of cementless TKA include preservation of bone stock (which potentially provides a better and more durable bone-implant interface), decreased operative time, avoidance of intramedullary pressurization and possible fat emboli, decreased soft tissue inflammation (thermal injury from curing cement), and carries no risk of mechanical cement failure. These advantages may have important positive benefits for longevity of TKA.

There are data suggesting that cementless components provide a more intimate relationship with bone that will increase the longevity of the implant interface and decrease the propensity for loosening of components. This becomes particularly important considering the increasing number of TKAs performed in younger patients. Demey et al.[25] showed a significant difference in radiolucent lines between cemented and cementless TKA. Gao et al.[26] also showed no difference in magnitude and pattern of migration of the femoral press-fit implant compared with cemented components as measured by radiostereometric analysis at two year follow-up.

There are a number of limitations associated with this study. First, the sample size was small and patients were recruited from a single surgeon. This did not allow for differences that may occur from varied surgical approaches and different prostheses, which could produce differences in results. Second, there was no strict control of physical therapy protocol, as patients were free to choose their therapist after leaving the hospital. In addition, no radiographic studies were utilized to look at implant fixation or osteolysis, and patients were not randomized to a specific treatment group. Furthermore, this study focused solely on the early functional outcome after TKA in terms of KSS and range-of-motion, but did not collect or evaluate the patient's daily function or subjective satisfaction with the procedure.

CONCLUSIONS

This study demonstrated that there was a significant early improvement in ROM for the cementless TKA group compared to the cemented TKA group, but no statistical significant difference in Knee Society Scores between both TKA groups. However, both TKA groups eventually reached similar ROM and KSS scores after a three-month, post-operative interval.

The findings of this study provided evidence that cementless TKA patients can undergo an identical post-operative protocol to cemented TKA, without concerns about implant stability or function.

ACKNOWLEDGEMENTS AND DISCLOSURE

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Keywords: orthopedics, total knee arthroplasty, treatment outcome

KANSAS JOURNAL of MEDICINE

CASE REPORT

Neuroleptic Malignant Syndrome Associated with Ischemic Injury of the Bilateral Basal Ganglia

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INTRODUCTION

Neuroleptic malignant syndrome (NMS) is an uncommon and potentially fatal untoward drug reaction associated with neuroleptic agents.[1] It presents with panoply of clinical manifestations including fever, muscular rigidity, altered sensorium, leukocytosis, and elevated serum creatinine kinase. Signs of autonomic instability such as tachycardia, hypertension, diaphoresis, and tachypnea also can be present. Together with supportive measures and the withdrawal of the offending agent, administration of the skeletal muscle relaxant, dantrolene, along with dopamine agonists, bromocriptine or amantadine, are necessary interventions in most cases. Although incidence is reported at only 0.02 to 3% in patients using neuroleptic medications,[2] mortality rates approach 10% and are related to complications arising from acute renal failure, acute respiratory failure, cardiac injury, and sepsis.[3] Therefore, preventions and identification of risk factors associated with NMS are crucial.

We present a patient with hypoxic-ischemic injury to the basal ganglia secondary to a provoked asthma attack who received the atypical antipsychotic, quetiapine, in rehabilitation and subsequently developed neuroleptic malignant syndrome.

CASE REPORT

A 48-year-old male asthmatic developed a hypoxic respiratory arrest. His past medical history was significant for severe asthma with frequent exacerbations. He had no neurologic history and was otherwise healthy. He was employed as a painter for a local vehicle resale company and endeavored to paint a project car at home without proper ventilation. Overcome by paint fumes, he developed a respiratory arrest and emergency medical services were contacted.

Upon their arrival, the patient was cyanotic and bradycardic. He entered asystole and treatment measures, in accordance with Advanced Cardiovascular Life Support guidelines, were administered with return of spontaneous circulation approximately six minutes after arrest. The patient was intubated and transferred to the intensive care unit (ICU). Upon extubation, he exhibited difficulties with speech, weakness in the right arm, cognitive and motor slowing, and agitation.

Magnetic resonance imaging (MRI) of the brain displayed diffusion restriction in bilateral cortical areas and basal ganglia, consistent with hypoxic injury (Figure 1). Due to agitation, he was placed on 50 milligrams of quetiapine and 50 milligrams of trazodone at bedtime. He slowly improved and was transferred to an inpatient rehabilitation facility.

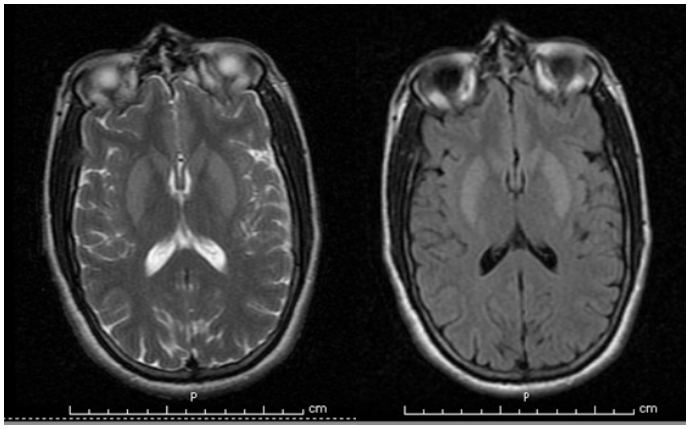

Figure 1. T2-MRI (left) and FLAIR MRI (right) taken within five days of the paitent's cardiopulmonary arrest revealed high signals involving the putamen and caudate bilaterally, indicating ischemia.

The patient was treated at the rehabilitation center for seven days, during which time quetiapine and trazodone were continued. Increased spasticity in his extremities developed and baclofen was added to his medication regimen, however, he experienced progressive tightness and rigidity of the extremities and decreased responsiveness. Tachypnea and a fever of 38.1°C developed. He was transferred to the ICU at an acute care hospital for evaluation of a possible infectious cause, none of which was found via imaging or laboratory studies.

The patient remained tachypneic, rigid, feverish, and became obtunded. Upon medication review, it was discovered that he was inadvertently given at least 100 milligrams of quetiapine and 50 milligrams of trazodone each evening at the rehabilitation facility for an unknown length of time. Given this information and the clinical picture, neuroleptic malignant syndrome was suspected. A repeat MRI of the brain showed evolution of the hypoxic changes in the basal ganglia (Figure 2). At this time, a neurology consultation was obtained and treatment with dantrolene and amantadine was initiated. The patient exhibited significant improvement within the first 24 hours of treatment, especially with muscle rigidity. Fortunately, there were no renal or cardiac complications from the event and most symptoms were resolved within one week.

His arousal and attention improved, but the hypoxic encephalopathy continued. On discharge, the patient returned to inpatient rehabilitation.

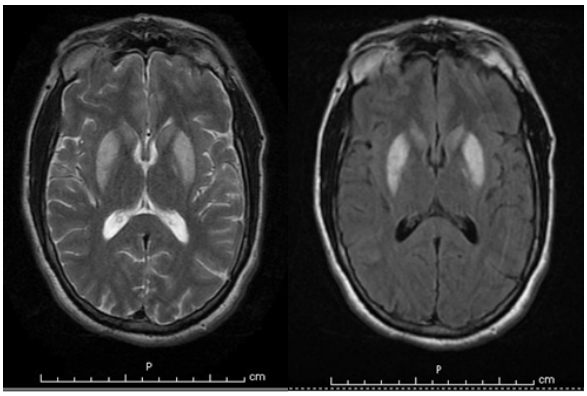

Figure 2. T2-MRI (left) and FLAIR MRI (right) taken approximately 19 days after arrest, showing evolution ischemic damage in bilateral basal ganglia.

DISCUSSION

Neurologic sequelae arising in survivors of cardiopulmonary arrest are a significant cause of morbidity. In acute ischemic stroke, cerebral hypoperfusion generally is confined to a focal vascular distribution, whereas in cardiac arrest, the lack of cerebral blood flow is global in nature, leaving the entire brain vulnerable to injury via both direct and reperfusion mechanisms. Areas especially prone to hypoxic injury include the cerebellum, hippocampi, cortex, and basal ganglia; all areas of high metabolic demand for oxygen and glucose.[4,5] Basal ganglia involvement has been described in neuroleptic malignant syndrome,[6,7] likely due to its dopaminergic neural circuitry involving the nigrostriatal pathways.[2]

Prior to receiving neuroleptics, our patient suffered from hypoxic-ischemic damage of the basal ganglia, particularly involving the putamen and caudate bilaterally, from a cardiopulmonary arrest. The cause of NMS is suspected to be due to excessive dopaminergic blockade within the brain, explaining the risks associated with antipsychotic agents, which act as dopaminergic antagonists. First generation antipsychotics are implicated more commonly than second generation, or "atypical," antipsychotics due to their higher affinity for dopamine receptors. However, both classes have been implicated in NMS. Additionally, high doses and rapid dose escalation of antipsychotic agents place patients at increased vulnerability to NMS.[8] Other factors also contribute to the development of NMS, such as preexisting central nervous system disorders, dehydration, and malnutrition.[9-12]

The blockade of dopamine in already damaged nigrostriatal dopaminergic circuits may have contributed to the emergence of NMS in this patient. To our knowledge, he had never been exposed to quetiapine in the past. During his hospitalization, he received a therapeutic dose of quetiapine daily but began receiving double the dose in error at rehabilitation before developing NMS. This error highlights the need for all medical facilities to have proper dosing precautions in place and effective medication administration.

CONCLUSION

We recommend that dopamine receptor antagonists should be used with caution or avoided in patients with hypoxic or ischemic injury to the basal ganglia, as the risk of further dopamine blockade could place the patient at risk for neuroleptic malignant syndrome. We also recommend early neurological consultation in patients with hypoxic-ischemic encephalopathy, as this may direct therapy and improve outcomes.

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Keywords: neuroleptic malignant syndrome, heart arrest, quetiapine fumarate

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Antiphospholipid Antibody Syndrome Causing Progressive Central Nervous System Dysfunction in a Young Patient

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INTRODUCTION

Antiphospholipid antibody syndrome (APS), also known as Hughes Syndrome, is an autoimmune disorder characterized by the presence of antiphospholipid antibodies (aPLs) and a hypercoagulability of blood which results in thrombotic events.[1] Diagnosis of definite APS, per the standards set forth by the International Congress on Antiphospholipid Antibodies, requires both clinical and laboratory corroboration.[2] Clinically, patients must present with one or more episodes of arterial, venous, or small vessel thrombosis and/or an adverse obstetric event such as spontaneous abortion. Laboratory findings must confirm elevated levels of any one of the following aPLs: lupus anticoagulant (LA), anticardiolipin antibody (aCL), or anti-β_2 glycoprotein-1 antibody.[2] This disorder can occur in association with systemic lupus erythematosus (SLE) or another rheumatic or autoimmune disease, however, approximately half of patients with APS show no evidence of a definable associated disease.[3] In the past, these two manifestations of the disorder have been referred to as secondary and primary APS, respectively, but the current preferred terminology is APS with or without associated rheumatic disease.[2]

The exact cause of APS and recurrent thrombosis is not clear, as the presence of aPLs alone is not sufficient for a diagnosis, with 1 - 5% of healthy individuals testing positive for aPL antibodies.[4] Furthermore, the clinical manifestation of APS tends to be heterogeneous as hypercoagulability and thrombosis can affect any organ system in the body. However, involvement of cerebral large vessels is frequent and, after venous thrombosis, the most common clinical symptoms of this disease tend to be transient ischemic attacks (TIAs) and stroke.[5] Other neurological manifestations can include chorea, epilepsy, multiple sclerosis-like lesions, psychiatric disorders such as depression and psychosis, migraine, and cognitive impairment.[6]

Cognitive abnormalities have been documented in individuals with elevated aPLs as well as APS.[7,8] Between 2 - 5% of patients with APS develop dementia or major neurocognitive impairment, while approximately 35% display mild to moderate cognitive impairment.[9,10] The most common cognitive difficulties tend to be in the domains of attention, verbal fluency, verbal learning, executive functioning, and short term memory.[11,12] Imaging of the brain, when available, often indicates diffuse and focal ischemic changes, cortical infarcts, and/or cerebral atrophy.[6,13]

The present case study outlines a woman with APS who developed psychiatric and motor-related issues, as well as progressive cognitive impairment, at a relatively young age. She underwent a neuropsychological evaluation in 2013 at the request of her neurologist.

CASE REPORT

The patient was a 41-year-old, right-handed, multi-racial female. Her educational history was significant for completing high school and trade school. She was employed until 2010 when she became disabled due to chronic fatigue and anxiety. At the time of the neuropsychological evaluation, she was living with her second husband of 2 ½ years.

The patient's medical history was significant for APS (diagnosed in 1998), chronic fatigue syndrome, multiple prior head injuries without loss of consciousness (secondary to physical abuse from her first husband) during the late 1990s to early 2000s, and a head injury with skull fracture and loss of consciousness (LOC; of approximately 24 hours according to records) secondary to a motor vehicle accident in 1989. The patient's psychiatric history was significant for depression and psychosis, which reportedly began in 2005. Because of her psychosis, she was psychiatrically hospitalized three times, with the most recent time being in 2012. She carried the following psychiatric diagnoses: Mood Disorder Not Otherwise Specified, Psychotic Disorder Not Otherwise Specified, and Dependent Personality Disorder. Her mood and psychotic disorders were thought to be the result of her APS. Family history was significant for a myocardial infarct in the patient's mother. The patient's medications at the time of the neuropsychological evaluation included paroxetine hydrochloride 20 mg, sulfamethoxazole and trimethoprim DS 800 - 160 mg twice daily, benztropine mesylate 1 mg, lamotrigine 50 mg, asenapine 10 mg, and acyclovir 200 mg as needed.

CLINICAL COURSE OF APS

The patient was diagnosed with APS at the age of 27 after her second miscarriage. Since that time, the patient has had multiple transient ischemic attacks secondary to this syndrome, the most recent of which occurred one month prior to the neuropsychological evaluation. Over the past eight years, the patient has had depression associated with psychosis, while over the past three years she has had worsening depression and a progressive decline in her motor and cognitive abilities. An MRI of the brain was conducted just prior to the neuropsychological evaluation

secondary to the patient's decline in functioning, and medical records indicated that the results showed "significant" cortical atrophy along with subcortical white matter changes (Figure 1). This reflected a recent change, as prior neuroimaging studies (CT from 2010 and MRI from 2008) did not reveal cortical atrophy and only showed chronic periventricular white matter disease. The patient also underwent a lupus work up, which revealed that her antinuclear antibody was positive at 1:640.

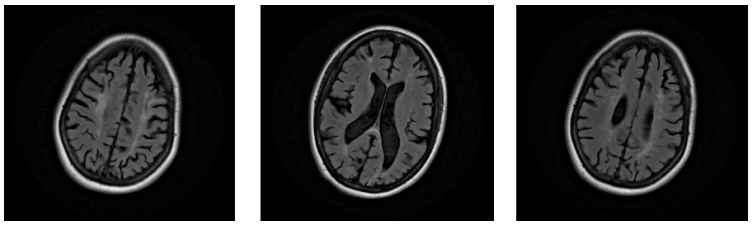

Figure 1. MRI of the brain showed "significant" cortical atrophy along with subcortical white matter changes.

CLINICAL PRESENTATION

As a result of the patient's progressive decline in functioning, she was referred for a neuropsychological evaluation. At the clinical interview, the patient's motor problems were reported to have caused reduced mobility in the patient's limbs and eye movements (the latter resulting in visual scanning difficulties). The patient and her husband indicated that she frequently stumbled and fell when walking, and her gait appeared to be unsteady. She reported her cognitive difficulties to be widespread, but short-term memory seemed to be the most affected, as she would forget what she was doing mid-task. An example provided by the patient's husband was that the patient once turned water on to do dishes, turned around to get things organized, forgot that she was going to do the dishes, and walked away with the water running. He also reported that the patient would forget to take her medications and that she stopped driving due to concerns about her ability to do so safely.

During the course of the evaluation, the patient demonstrated difficulty recalling details of her background and medical history including when her symptoms began. While she was able to comprehend casual interview questions, she required repetition and elaboration of formal test instructions to comprehend them. Her speech was slow in rate, somewhat soft in volume, and occasionally mildly disarticulate. Thought processes were slow but generally logical and coherent. However, perseveration was noted at times during the testing session. There was no evidence of delusions or hallucinations, but the patient noted that she recently had been experiencing some degree of paranoia. Affect was somewhat dysphoric. Mood was described as fluctuating based on the weather. Psychomotor retardation was evident. Insight into her cognitive functioning was impaired.

Neuropsychological testing was valid based on the patient's performance on empirically-derived validity tests. Premorbid intellectual abilities were estimated objectively to be in the average range of functioning (estimated IQ = 102; 55th percentile). This was calculated by entering the patient's demographic variables (i.e., age, sex, ethnicity, and level of education) and performance on a word reading task into an established predictive equation.[14] To measure the patient's current intellectual functioning, she was administered the Wechsler Abbreviated Scale of Intelligence - Second Edition, which yielded an Intelligence Quotient of 69 (2nd percentile), a significant decline in intellectual functioning of two standard deviations and a change from "average" to "deficient."

The Repeatable Battery for the Assessment of Neuropsychological Status was administered to examine a range of current neurocognitive functions. This measure is composed of 12 subtests that assess verbal and visual learning and memory, visuospatial abilities, expressive language abilities, mental processing speed, and simple attention span. The patient's performance was moderately to severely impaired (< 1st percentile) on all subtests with the exception of two: a measure of visuospatial line orientation (mildly impaired, 7th percentile) and a measure of confrontation naming (average, 30th percentile). The Brief Visuospatial Memory Test - Revised was administered as an assessment of visuospatial learning and memory. Again, the patient's performance was moderately to severely impaired (< 1st percentile).

The Delis-Kaplan Executive Functioning System was administered as a measure of higher-level cognition including sustained attention, set-shifting, inhibition, and mental flexibility. Across these tasks the patient's performance was moderately to severely impaired (< 1st percentile). Measures of finger tapping, grip strength, and grooved pegboard also were administered to assess the patient's motor control and manual dexterity. Finger tapping and grooved pegboard had to be discontinued due to psychomotor retardation, spasticity, and poor coordination, particularly with the non-dominant (left) hand. Grip strength was bilaterally impaired but the non-dominant (left) hand was significantly weaker than the dominant (right) hand. Finally, brief depression and anxiety screening tests indicated that the patient was experiencing moderate levels of both conditions.

DISCUSSION

The incidence of dementia or major neurocognitive disorder secondary to APS is rare in the literature, with only a small percentage of patients subsequently developing severe cognitive problems.[9,10] In the current case, comprehensive neuropsychological data were presented on a relatively young patient with APS who was thought to have developed major neurocognitive impairment, in addition to psychiatric and motor-related symptomology, due to her APS. Neuropsychological testing showed essentially global cerebral impairment, resulting in significant deficits in intellectual functioning, attention, mental processing speed, verbal fluency, visuospatial ability, learning and memory, executive functioning, and bilateral motor functioning. When compared to neurologically healthy age-matched individuals, this patient's scores were consistently at or below the 1st percentile. The only test score that was

not within an impaired range of functioning was a score from a confrontation naming test. However, this test has been criticized as it has been shown to have minimal sensitivity to cognitive dysfunction even in patients with neurodegenerative dementia processes.[15-17] Overall, it was concluded that neuropsychological testing provided strong evidence of a significant and essentially global central nervous system abnormality.

Because the patient has a history of head trauma, the possibility that her symptoms might have resulted from this head trauma, instead of APS, should be addressed. The patient's history of head trauma was not a primary contributor for numerous reasons. The patient's head injury with skull fracture occurred in 1989, her other head injuries (due to physical abuse) occurred in the late 1990s to early 2000s, and no additional head injuries occurred after that date. These head injuries were not thought to have resulted in any significant, longstanding cognitive difficulties, as the patient continued to work successfully as a hairdresser until 2010. Neither she nor her husband reported any significant cognitive difficulties until 2010. Furthermore, an MRI of the brain from 2008 and a CT of the head in 2010 showed no cortical atrophy and only mild chronic periventricular white matter disease. Thus, there was no evidence of any significant cognitive or neurologic dysfunction predating 2010, and there was no evidence of significant residual cognitive deficits from the prior head trauma.

In 2010, the patient began having more TIAs and her husband noticed increased cognitive, motor, and psychiatric issues. These issues progressed over time and an updated MRI of the brain, conducted in 2013, showed "significant" cortical atrophy along with subcortical white matter changes (Figure 1). Given that the onset of the patient's symptoms corresponded with an increase in TIAs (which are common in APS),[5] that updated neuroimaging showed cortical atrophy and subcortical white matter changes (which is not uncommon in APS),[6,13] that the progressing symptoms included increased cognitive, psychiatric, and motor abnormalities (all of which are common in APS),[6] and that the patient was relatively young and physically healthy outside of her APS-related symptomatology, and had no other significant risk factors for early-onset dementia, it was concluded that this patient's dementia very likely was due to the progression of her documented APS.

Due to the degree of cognitive impairment resulting from her dementia, a recommendation for supervision and assistance with daily activities, like driving a motor vehicle, was proposed. Additional recommendations included pursuing legal counsel to set up surrogate decision-making responsibilities (e.g., guardianship and conservatorship).

Unfortunately, the patient's prognosis was poor given the etiology and nature of her documented symptoms. Once dementia occurs, there are no treatments to reverse the cognitive impairments. Management of APS typically focuses on controlling other symptoms that are a consequence of the disease (e.g., psychiatric disturbances and motor symptoms).[18] For those patients who experience ongoing episodes of thrombosis, stroke, or transient ischemic attacks, the administration of anticoagulants and immunosuppressive drugs usually is recommended, although randomized controlled trials investigating the effectiveness of these drugs are limited.[19] Thus, evidence to suggest that these medications may prevent or delay the development of cognitive dysfunction is lacking.

At the time of the patient's neuropsychological evaluation, she was not taking any anticoagulant or immunosuppressive drugs, nor did she report past prescriptions of these medications. It is possible that the outcome of her case could have been different if such medications had been prescribed. There is not, however, a simple linear relationship between the development of cognitive dysfunction and a history of central nervous system complications in APS.[10] For example, in a study among patients with APS, three patients under the age of 30 developed dementia without a history of cerebrovascular accidents.[20] Other researchers also have cited examples of patients with APS who displayed chorea or mild cognitive impairment, but had no focal lesions on imaging.[21,22] Due to these findings, it has been suggested that the disease mechanism that leads to the development of cognitive impairment secondary to APS is more complex and cannot be explained solely by the occurrence of repeated cerebrovascular events. Other proposed ways through which APS can lead to cognitive dysfunction includes the role of aPL antibodies in the inhibition of astrocyte proliferation and disruption of vascular endothelium.[23,24] As a result, it is impossible to say whether this patient would have had some degree of cognitive decline if she would have been prescribed anticoagulants or immunosuppressive drugs prior to her recurrent cerebrovascular events. Nonetheless, aggressive preventative treatment should be considered in APS patients, especially when patients report having a history of cerebrovascular events and/or cognitive changes.

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Keywords: antiphospholipid antibody syndrome, Hughes Syndrome, central nervous system

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Exercise-Associated Hyponatremia in Cystic Fibrosis

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INTRODUCTION

Cystic fibrosis (CF) is a full body, multi-system disease resulting from dysfunctional chloride ion transport across the cell membrane because of a dysfunctional Cystic Fibrosis Membrane Conductance Regulator (CFTR) protein.[1] While pulmonary and pancreatic dysfunction are its classic phenotype, the sweat glands also are affected significantly, and sweat chloride testing remains a gold standard in the diagnosis of CF. Alongside high sweat chloride concentrations, those with CF also experience elevated sweat sodium concentrations and, therefore, the potential to lose meaningful amounts of sodium chloride in their sweat.

Focusing on what has been described as "voluntary dehydration" due to a theorized lower thirst drive within the CF population, non-evidence based recommendations[2] have been to drink beyond level of thirst and to increase consumption of sodium via salty foods to attenuate body sodium loss and maintain volume within the vascular space.[3] Concern with this advice arises with the observation of the well-established body of evidence demonstrating overconsumption of fluids to be the major contributing factor in the development of exercise-associated hyponatremia (EAH), a phenomenon whose incidence increased alongside "drink beyond one's thirst" advice within the general athletic community.[4] The following case demonstrates the point at which CF and EAH meet and describes how the current fluid intake recommendations and the lack of evidence-based sodium replacement guidelines in the CF community may function to increase the risk of hyponatremia rather than achieving the intended goal of preventing dehydration.

CASE REPORT

In 2015, a 36-year-old female with CF status-post lung transplantation at age 22, was hiking in the Grand Canyon with a friend. In the nine years since transplantation, her forced expiratory volume in 1 second (FEV1) averaged 70% and she routinely was active on a daily basis. Temperature during the hike ranged from 60 to 85 degrees Fahrenheit. The descent took 2.5 hours, and they took a 30-minute rest in the shade. The ascent took 1.5 hours. The patient recalled feeling progressively "unwell". Her self-assessment was that of dehydration since the symptoms of nausea, dizziness, confusion, and weakness were consistent with dehydration she had experienced in the past. She stopped to urinate several times during the hike. The US National Park Service described the route as three miles, round trip with an elevation difference of 1,140 feet between these points on the trail.[5]

After a 10 minute rest, they boarded a shuttle bus where she vomited "copious amounts of clear water into a bag" and required assistance to get off the bus. Her vision deteriorated to where she was "only able to see colors and no discernible shapes". She did not remember walking to the car, but recalled her friend "depositing" her into the front seat. At this point, she lost consciousness. Her next memory was waking up intubated in a hospital intensive care unit (ICU).

When she lost consciousness, her friend drove her to a local clinic where she communicated with the staff but was combative. From the available medical records, the Glasgow Coma Score (GCS) was 6, and on-site serum sodium was 126 mmol/L. The physician at the clinic ordered 300 mL of intravenous (IV) 3% saline as the patient was prepared for transport by helicopter to an appropriate facility. Upon arrival in the emergency department (ED), her blood pressure was 137/95 mmHg, heart rate was 82 bpm, respiratory rate was 18 bpm, oxygen saturation on room air was 93%, and her GCS had improved to 12. Additional indications of volume status in the medical record included extremities described as "warm and well perfused" and "without edema." She remained intermittently somnolent and combative, and serum sodium persisted at 126 mmol/L. Computed tomography (CT) of the head suggested diffuse cerebral edema but was otherwise un-interpretable from motion artifact, and magnetic resonance imaging (MRI) was recommended. Due to unchanged mental status and continued hyponatremia, an additional 100 mL of 3% hypertonic saline was given. Repeat serum sodium, 7 - 8 hours after presentation, was 127 mmol/L so a 3% saline IV drip was initiated at 40 mL/hr. She was intubated and sedated due to combativeness and inability to cooperate with the MRI. MRI demonstrated no acute changes.

In the ICU, serum sodium rose to 130 mmol/L after eight hours of 3% saline therapy. GCS was 13 - 14 and the 3% infusion rate was decreased to 10 mL/hr. Over the following 10 hours, serum sodium drifted to 135 mmol/L and hypertonic saline was changed to normal saline. The patient was extubated the next day and, at 22 hours after presentation, serum sodium was 137 mmol/L. She was discharged around 48 hours after presentation. In all, the patient received 820 mL of IV 3% saline during the first 24 hours.

In the ED, this patient's serum osmolality was 274 mOs/kg while serum sodium was 126 mmol/L.

After receiving 820 mL of 3% saline, osmolality was 287 mOs/kg with a sodium of 135 mmol/L. Ten hours after hypertonic saline had been switched to normal saline, osmolality was 291 mOsm/kg with a sodium of 138 mmol/L. Urine studies were not performed and weight changes were not in the available records. Her condition most likely demonstrated a free water intoxication state that corrected with fluid restriction and osmolar load supplementation with a subsequent free water diuresis that lead to the improvement in serum sodium.

She did not recall being given more specific recommendations for hydration and sodium intake from the CF community than that she "can't hydrate enough" and that she needs to eat salty foods. On the day of the hike, she was not concerned about replacing lost sodium, and the emergency department record indicated that she had consumed 3 - 5 liters of fluid prior to and during the hike. The patient confirmed that she consumed more than was typical for her in anticipation of the low humidity and heat. In addition, she described not feeling thirsty during the hike. Her solute intake amounted to a breakfast of eggs and bacon, beef jerky, trail mix, and a few salted peanuts.

DISCUSSION

The standard recommendation for preventing dehydration in patients with CF has been to drink fluids before thirst develops and to continue drinking beyond the level of thirst.[2] The standard recommendation for sodium replacement has been to increase ingestion of salty foods and to add salt to fluids ingested.[3] These recommendations lack emphasis on the importance of balancing fluid and sodium intake for those with CF and may increase the risk of hyponatremia. Exercise-associated hyponatremia is a well-defined condition, known to occur when fluid ingestion is out of balance with water excretion, and can be thought of as existing along a spectrum with pure overconsumption of fluids on one end (more common) and the overconsumption of fluid relative sodium loss on the other (more rare).[4] Additional factors that are known to contribute in the development of EAH are the persistent secretion of antidiuretic hormone (ADH), the inability to utilize internal stores of exchangeable sodium and, in individuals with pathologically high sweat sodium concentrations, sweat sodium loss.[4] This patient's fluid intake was likely excessive along with an osmolar intake that was insufficient. If she had followed the evidence-based recommendation on drinking to thirst that is gaining traction in the non-CF community,[4] she possibly could have avoided developing hyponatremia altogether.

CF patients should be counseled to consider thirst drive rather than drinking beyond it. Brown et al.[6] compared cohorts of healthy individuals with normal sweat sodium, healthy individuals with elevated sweat sodium, and CF patients by measuring thirst perception during exercise to 3% dehydration (based on % body weight loss) without drinking. While plasma volume decreased and serum osmolality increased according to sweat sodium losses, thirst response was identical in all three cohorts at all levels of dehydration. Exercise time to 3% dehydration varied by only eight minutes across cohorts, and total body water loss and sweat rates also were statistically similar. The CF cohort, however, had meaningful lower free water losses. During recovery, the CF cohort consumed 40% less fluid ad libitum, a demonstration of the "involuntary dehydration" principle in CF.[2] Even so, 40 minutes into recovery, they demonstrated a decrease in serum sodium relative to baseline and were allowed salty foods against protocol. While serum sodium did not drop below 135 mmol/L, they were below baseline two hours into recovery.[5]

CONCLUSION

This case demonstrated that the "involuntary dehydration" behavior in CF may originate in its protective effect against hyponatremia and that the non-specific recommendations for fluid and sodium replacement in the CF community may not be adequate.[6] This patient reported not feeling thirsty during the hike. EAH likely could have been avoided if she observed her level of thirst and consumed fluid accordingly rather than consuming beyond thirst to avoid dehydration and had more specific sodium replacement guidelines available. In an era where CFTR modulators are available for an increasing number of CF patients,[1] it is imperative that evidence-based guidelines for fluid intake and sodium replacement be developed to address hypovolemia and EAH in this population. With the hope of leading a more normal life, those with CF may be at risk for developing EAH and its potentially devastating effects as they become more active.

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Informed, written permission from the subject of this Case Report is on file with the corresponding author.

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Keywords: cystic fibrosis, hyponatremia, dehydration, hypovolemia

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Listen to the Patient: A Case Report and Literature Review of DRESS

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INTRODUCTION

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a rare, potentially life-threatening, drug-induced hypersensitivity reaction that includes skin eruption, hematologic abnormalities (eosinophilia, atypical lymphocytosis), lymphadenopathy, and internal organ involvement.[1-3] DRESS initially was observed in patients treated with anticonvulsants in the early 1930s, when phenytoin first became available.[4] Many clinical terms have been used to describe DRESS, including hypersensitivity syndrome and mononucleosis-like syndrome.[2] In 1996, Bocquet et al.[1] proposed the term DRESS "to decrease the ambiguity of the denomination of hypersensitivity syndrome" and to give a more accurate description of this clinical syndrome. The incidence of DRESS ranges from 1 in 1000 to 1 in 10,000 drug exposures.[5]Aromatic anticonvulsants (especially phenytoin, carbamazepine, and phenobarbital) and sulfonamides (such as dapsone and sulfasalazine) are the most common causes of DRESS.[1,6]

This case report and review revisits the association between sulfasalazine and DRESS and reminds clinicians to consider this entity as part of a broad differential diagnosis when evaluating patients who experience unusual clinical manifestations after starting this culprit medication.

CASE REPORT

A 46-year-old African American female with Crohn's disease, complicated by enterocutaneous fistulas and status-post small bowel resection, acid reflux, and chronic migraines presented in early 2016 for new onset rash involving her face, arms, abdomen, and upper thighs. She had seen her rheumatologist 1.5 weeks prior to admission, at which time she was started on sulfasalazine. Her primary care physician around the same time had started her on ranitidine for acid reflux. Both agents were stopped prior to admission, but the rash persisted. She also was taking amitriptyline, cetirizine, citalopram, cyclobenzaprine, diclofenac gel, diphenhydramine, ergocalciferol, fluticasone, lidocaine patch, morphine SR, ondansetron, and oxycodone as needed. She was not on steroids prior to arrival.

On admission, she was febrile, tachycardic, tachypneic, and appeared ill. She had an erythematous, pruritic, maculopapular rash involving her face, arms, abdomen, and upper thighs without drainage. No abscesses were noted. Her labs revealed a sodium level of 125 mmol/L (low), a total bilirubin of 2.5 mg/dL (high), an alkaline phosphatase of 136 U/L (high), a lactate of 2.7 mmol/L (high), white blood cell count of 5,800/mcL, platelet count of 123,000/mcL, hemoglobin of 11.8 gm/dL (low), and 18% "other cells". Peripheral smear revealed reactive and atypical lymphocytes with mild monocytosis. LDH was elevated at 500 U/L, haptoglobin was low at < 30 mg/dL, and reticulocyte count was elevated; all consistent with acute hemolysis. The acute hepatitis panel was negative.

She initially was started on broad-spectrum antibiotics for suspected severe sepsis of undetermined etiology in the setting of chronic immunosuppression from Crohn's disease. The other differentials on admission were drug reaction versus DRESS. Dermatology initially was unconvinced about the diagnosis of DRESS since the patient's rash did not fit the typical chronological pattern consistent with DRESS. It had been only 1.5 weeks since she had begun the suspected medications.

Hematology was consulted due to the patient's hemolytic anemia. A Coomb's test, plasma free hemoglobin, and G6PD test were within normal limits. Flow cytometry revealed reactive T cell lymphocytosis. The patient had an abdominal ultrasound which showed a peripheral splenic infarct. Infectious disease tested for an Epstein-Barr virus (EBV), cytomegalovirus, human herpesvirus 6, parvovirus B19, and adenovirus PCRs, HIV antigen/antibody, and syphilis and Cryptococcus antigens. Only the EBV panel was positive. Other pertinent negative tests included ceruloplasmin, anti-neutrophil cytoplasmic antibodies, anti-Saccharomyces cerevisiae antibodies, antimitochondrial antibody, antinuclear antibody, and alkaline phosphatase.

The patient developed severe facial edema within a few days of admission. Otolaryngology performed a flex exam revealing no oropharyngeal or supraglottic swelling and a patent airway. Biopsy performed by dermatology was most consistent with DRESS and showed no evidence of Stevens Johnson syndrome or toxic epidermal necrolysis. Dermatology suspected the culprit drug was sulfasalazine over ranitidine. Antibiotics were discontinued at that time and high-dose systemic corticosteroid therapy was initiated (prednisone 80 mg daily). She also was started on a proton pump inhibitor, calcium, vitamin D supplementation, and dapsone for prophylaxis for Pneumocystis jiroveci pneumonia (PJP) while on a prolonged systemic corticosteroid course.

Aerosolized pentamidine and atovaquone were discussed with the patient but dapsone was considered best option due to cost. Dapsone can cause DRESS, but the patient was initiated on high-dose systemic corticosteroid therapy and the risk for PJP was deemed very high.

There was a risk-benefit discussion with the patient and she elected to take dapsone therapy. The patient's symptoms markedly improved and she had appropriate follow-up. The patient did well on dapsone therapy and did not develop any complications.

DISCUSSION

This patient's symptoms and clinical findings were difficult to interpret on admission. First, the onset of symptoms with DRESS typically occurs two to six weeks after drug administration. Our patient's symptoms started only 1.5 weeks after starting sulfasalazine. Second, there was no evidence of peripheral eosinophilia or facial edema on admission (although she experienced facial edema later in her course). Last, there was no evidence of an elevated serum alanine aminotransferase (ALT) level. Despite the atypical time course, our patient's rash started 1.5 weeks after a culprit drug (sulfasalazine) was initiated. Statistically speaking, sulfasalazine (and less likely ranitidine) was considered to be the cause of DRESS in this patient since sulfasalazine has been implicated in 10 cases according to the RegiSCAR's Score and ranitidine was not included.[7] Ranitidine is even labeled as a "miscellaneous cause" by Criado et al.[8]

In approximately 30% of cases, there is eosinophilia in DRESS syndrome but it can be delayed for one to two weeks.[1,9] Liver abnormalities with elevated serum ALT are found in approximately 70% of patients with DRESS syndrome, although one series of 27 patients found it in more than 95% of them.[10,11] The most common skin biopsy findings are a dense, perivascular lymphocytic infiltrate in the papillary dermis, with the presence of extravasated erythrocytes, eosinophils, and dermal edema.[2] Our patient's skin biopsy revealed a perivascular lymphoid infiltrate with rare neutrophils and extravasated erythrocytes.

According to RegiSCAR diagnostic criteria,[12] our patient met criteria for DRESS. The patient must: 1) have an acute rash, 2) have drug-related symptoms, 3) require hospitalization, and three of the following four signs: fever > 38C, enlarged lymph nodes involving > 2 sites, involvement of > 1 internal organ, and blood count abnormalities. Final scores: < 2: excluded; 2 – 3: possible; 4 – 5: probable; > 5: definite.[13] The diagnosis of DRESS should be suspected with the presence of skin rash, liver involvement, hyper-eosinophilia, and lymphadenopathy in the setting of fevers. The standard of care is to stop the suspected causative agent and initiate systemic corticosteroids. Systemic corticosteroids are the current mainstay of treatment. A recommended starting dose is 1.0 – 1.5 mg/kg/day of prednisone or an equivalent drug and this dosage should be slowly tapered over 6 - 8 weeks to avoid a flare-up of symptoms.[14] Further studies are needed to recommend specific treatment guidelines.

CONCLUSION

Often in medicine, physicians are confronted with diagnostic dilemmas. Our case highlighted the importance of the history and physical examination in maintaining a broad differential and making an accurate diagnosis. Internists must be aware of DRESS and its common culprit medications, as it is a potentially fatal diagnosis if left untreated. Prompt diagnosis is important to treat the underlying disease process.

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Keywords: drug reaction with eosinophilia and systemic symptoms syndrome, drug hypersensitivity syndrome, sulfasalazine

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CEA as a Marker for Medullary Thyroid Carcinoma in a Patient with Colorectal Cancer

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INTRODUCTION

Carcinoembryonic antigen (CEA) is a protein involved in cell adhesion.[1] First described by Gold and Freedman,[2] CEA measurement is used as a tumor marker to monitor colorectal carcinoma treatment, identify recurrences after surgical resection, and stage or localize cancer spread through measurement of biological fluids.[3] Rarely, CEA elevation can be associated with other malignancies and disorders. In this report, a middle-aged man with a history of colon cancer presented with persistently elevated CEA after presumptive remission.

CASE REPORT

A 56-year-old male with poorly controlled hypertension and glycemia presented with recurrent episodes of pressure sensation in his chest, profuse sweating, and flushing for the past few months. Past medical history was significant for left adrenal pheochromocytoma status post left adrenalectomy 10 years prior and colon cancer status post partial colectomy followed by chemotherapy with persistent CEA elevation of 400s ng/ml (normal range 0.0 - 4.7 ng/ml). Further testing, including whole body CT scan, PET scan, and gastrointestinal scopes, failed to localize colon cancer recurrence. Physical examination revealed a palpable hard, non-tender nodule in the left mid-antero-lateral compartment of the neck.

Laboratory testing showed elevated 24-hour urinary metanephrines with a markedly abnormal serum calcitonin level of 7735 pg/ml (normal range is 10 pg/ml or less). CT scan of the abdomen confirmed a right adrenal nodule with positive uptake on a metaiodobenzylguanidine (MIBG) scan. Thyroid sonography showed a calcified thyroid node in the left mid-antero-lateral compartment of the neck. Genetic testing confirmed a mutant RET oncogene, confirming the clinical suspicion of multiple endocrine neoplasia syndrome type 2A (MEN 2A).

Right adrenalectomy was performed, revealing an 8.5 cm tumor located in the adrenal medulla, consistent with pheochromocytoma. Total thyroidectomy followed consistent with multifocal medullary thyroid carcinoma (MTC) and 18/18 lymph nodes with metastatic medullary carcinoma. However, calcitonin was elevated persistently on routine follow-up after the surgery with 10250 pg/ml and CEA of 187 ng/ml. The follow-up measurements, a year later, were 9242 pg/ml and 160 ng/ml for the calcitonin and CEA, respectively. Of note, the patient's daughter also was diagnosed with MTC at the age of 16 after prophylactic thyroidectomy was performed.

DISCUSSION

Although of minimal use in detecting early colorectal cancer, high preoperative concentrations of CEA correlate with adverse prognosis.[4] Serial CEA measurements can detect recurrent colorectal cancer with a sensitivity of 80% and a specificity of 70%.[5] CEA is the most frequent indicator of recurrence in asymptomatic patients.[6,7] CEA levels also may be raised in medullary thyroid carcinoma[8] as well as some non-neoplastic conditions like cirrhosis[9] and hypothyroidism,[10] as well as in smokers.[11]

History of bilateral pheochromocytoma, a thyroid mass, markedly elevated serum calcitonin level, and a persistently elevated CEA with a normal yearly colonoscopy, suggests that the elevated CEA, in this case, was due to MTC. CEA level also was found to be correlated with progression and prognosis of the MTC. A CEA level of less than 30 ng/mL is consistent with local MTC and surgery might be curative in this situation. Levels more than 30.0 ng/mL indicate central and lateral (ipsilateral) lymph node metastases, whereas CEA levels more than 100.0 ng/mL suggest lateral (contralateral) lymph node metastases and distant metastasis.[12] CEA has additional importance in this specific disease as preoperative CEA levels may be helpful for determining the invasiveness of the surgery, the extent of lymph node dissection, thus the prognosis in patient with MTC.[12]

CONCLUSION

Patients with colorectal carcinoma often have higher levels of CEA (above approximately 2.5 ng/mL) than healthy individuals.[13] CEA commonly is used to identify recurrences after surgical resection.[3] Bilateral pheochromocytoma, a thyroid mass, markedly elevated serum calcitonin level, and a persistently elevated CEA favored the diagnosis of MEN 2A syndrome over recurrence of colon cancer. In cases with persistently elevated CEA with non-significant colonoscopies, suspicion should be high for other causes, especially if patient presentation was consistent with signs and symptoms of MEN 2 syndrome. Also, CEA signals the extent and the site of metastases and subsequently the surgical invasiveness.

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Keywords: carcinoembryonic antigen, medullary thyroid cancer, MEN 2A syndrome

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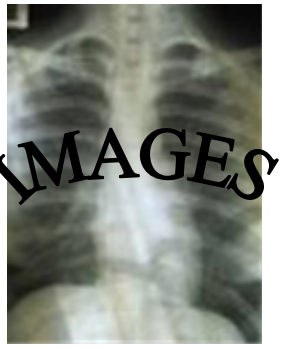

Zoster Ophthalmicus with Zoster Meningoencephalitis

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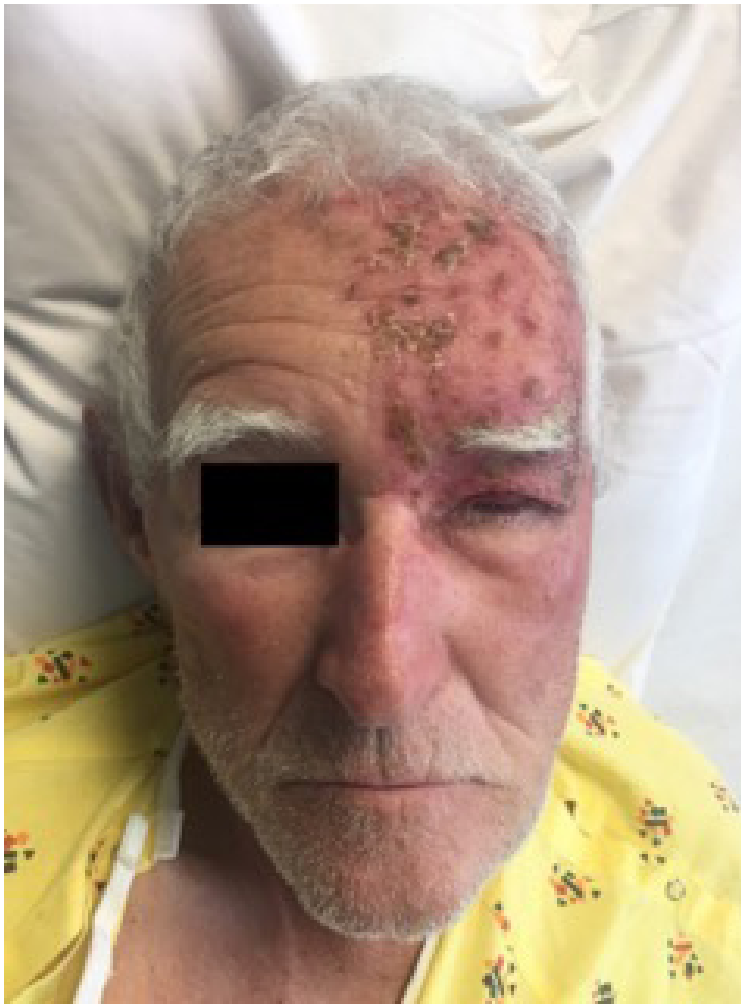

An 82-year-old man presented to the hospital for severe confusion with left-sided facial rash for six days. He was seen by his primary care physician when the rash began and was started on oral acyclovir. He had never received vaccination against varicella zoster virus (VZV). He experienced multiple falls, worsening confusion, and deteriorating visual impairment of the left eye and he was brought to the hospital for further evaluation. On examination, he was disoriented to time and place, and family noted the patient to be experiencing intermittent visual hallucinations. He had a vesicular rash on an erythematous base with crusted lesions limited to the V1 distribution of the left trigeminal nerve. The left eyelids were edematous, and were unable to be opened, with conjunctival exudate. He was changed to IV acyclovir. Lumbar puncture was performed with cerebrospinal fluid (CSF) findings significant for 340 leukocytes/mm3, 25% lymphocytes, 71% monocytes, protein of 229 mg/dl, and glucose of 42 mg/dl. Rapid VZV PCR was positive. He was diagnosed with zoster ophthalmicus complicated by meningoencephalitis. His mental status, rash, and visual acuity subsequently began to improve on IV acyclovir. He was continued on IV acyclovir for two weeks and had full recovery.

DISCUSSION

The incidence of zoster ophthalmicus is estimated to be 30.6 per 100,000.[1] Ocular complications include keratitis, corneal inflammation, uveitis, and eventually blindness which can occur in up to two-thirds of patients with late stage disease at presentation.[2] Almost half of patients with zoster ophthalmicus can have CSF pleocytosis, and near one-third can have positive VZV, even without symptoms of meningitis.[3] Monocytosis of the CSF is typical for VZV infection.[4] IV acyclovir has the best CSF penetration and is recommended for those with neurologic symptoms.[5] Lumbar puncture should be performed in zoster ophthalmicus if there is high clinical suspicion as it influences route and duration of therapy.[4] The Infectious Disease Society of America recommends treating VZV encephalitis with IV acyclovir at a dose of 10 - 15 mg/kg every eight hours for 10 - 14 days.[6]

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Keywords: herpes zoster ophthalmicus, varicella encephalitis, herpes zoster meningoencephalitis

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