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研究成果の刊行に関する一覧表

雑　誌

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Correlations of adiponectin level with insulin resistance and atherosclerosis in Japanese male populations

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Summary

OBJECTIVE Adiponectin, which is secreted specifically by adipose tissue, has been shown to have an anti-atherosclerotic effect and to improve insulin resistance. The aim of this study was to determine the correlations of plasma adiponectin concentration with insulin resistance and atherosclerosis.

DESIGN AND METHODS We investigated the relationships of adiponectin concentration with insulin sensitivity, high-sensitivity C-reactive protein (hCRP) and pulse wave velocity (PWV) in male inhabitants of rural communities in Japan. hCRP and PWV were used as an indexes of atherosclerosis.

RESULTS A negative correlation was found between homeostasis model assessment (HOMA) as an index of insulin resistance and adiponectin concentration. Results of stepwise regression analysis for adiponectin showed that age, HOMA and serum triglyceride (TG) were independently correlated with adiponectin. Multiple regression analysis for lipid profile was also performed and revealed that adiponectin and HOMA were independently correlated with TG and serum high density lipoprotein (HDL)-cholesterol but not with serum total cholesterol. A significant negative correlation was found between adiponectin and hCRP in all subjects, and a significant negative correlation between adiponectin and PWV was also found in subjects equal or less than 70 years old. When HOMA was added to this analysis, HOMA was found to be independently correlated with hCRP and PWV, but the adiponectin level did not appear to be a significant predictor of hCRP or PWV.

CONCLUSIONS The results suggest that adiponectin plays a role in lipid metabolism and correlates with atherosclerosis either directly or through insulin resistance.

Several prospective epidemiological studies have suggested that there is an association between insulin resistance and/or hyperinsulinaemia and subsequent cardiovascular disease and stroke (Despres *et al.*, 1996; Haffner, 1999). We have previously demonstrated that insulin resistance and hyperinsulinaemia are important risk factors for coronary artery disease (CAD), and emphasize the severity of coronary atherosclerosis in patients without impaired glucose tolerance but with hyperinsulinaemia (Tsuchihashi *et al.*, 1999). Recently, because of the epidemic of overweight and sedentary lifestyle worldwide, the metabolic syndrome, a concurrence of disturbed metabolism, overweight and abdominal fat distribution, mild dyslipidaemia and hypertension, is becoming increasingly common. According to the National Cholesterol Education Program (NECP) definition (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001), roughly one-third of middle-aged men and women in the United States have the metabolic syndrome (Ford *et al.*, 2002). Lakka *et al.* (2002) have recently reported that men with the metabolic syndrome as defined by the NCEP were 2·9–4·2 times more likely to die of coronary heart disease after adjustment for conventional cardiovascular risk factors. The pathogenesis of this syndrome is still unclear, although environmental factors such as diet and physical activity interact to produce the syndrome.

Adipose tissue not only serves as an energy storage organ but also secretes hormones and metabolites that are thought to regulate insulin sensitivity and energy metabolism (Kahn & Flier, 2000; Havel, 2002). Adiponectin, the most abundant adipose-specific protein, is expressed exclusively in and secreted from adipose tissue (Scherer *et al.*, 1995). Plasma adiponectin concentration is decreased in individuals with obesity (Arita *et al.*, 1999) and type 2 diabetes (Hotta *et al.*, 2000) and is more closely related to whole-body insulin sensitivity than to adiposity (Weyer *et al.*, 2001). Conversely, body-weight reduction increases plasma concentration of adiponectin (Yang *et al.*, 2001). It has also been reported that adiponectin-deficient mice develop diet-induced

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insulin resistance (Maeda *et al.*, 2002). Recent studies have demonstrated that administration of adiponectin to rodents increased insulin-induced tyrosine phosphorylation of the insulin receptor in skeletal muscle, resulting in improved glucose tolerance (Yamauchi *et al.*, 2001). In a human study, it was found that low adiponectin concentration at baseline preceded a decrease in muscle tyrosine phosphorylation of the insulin receptor by insulin (Youngren *et al.*, 1997). Adiponectin has also been proposed to play an important role in the regulation of energy homeostasis and lipid metabolism. High levels of serum triglyceride (TG) and low levels of high density lipoprotein (HDL)-cholesterol are associated with low plasma adiponectin concentrations in nondiabetic female subjects (Matsubara *et al.*, 2002). Moreover, recent studies have suggested that adiponectin has not only an anti-inflammatory effect on the vascular wall (Okamoto *et al.*, 2000) but also an anti-atherosclerotic effect by direct actions on endothelial cells (Ouchi *et al.*, 1999; Kubota *et al.*, 2002). Clinical studies have shown that adiponectin levels are lower in individuals with CAD (Ouchi *et al.*, 1999). However, relationships between adiponectin level and the development of atherosclerosis and metabolic disorders, including insulin resistance, are still obscure.

Aortic stiffness increases with aging and arterial pressure elevation and in patients with CAD (Boutouyrie *et al.*, 2002). Aortic stiffness can now be assessed noninvasively by measurement of pulse wave velocity (PWV), a simple and reproducible method (Asmar *et al.*, 1995). Recent longitudinal studies have demonstrated that PWV is an independent predictor of all causes and cardiovascular mortality in patients with end-stage renal disease (Blacher *et al.*, 1999) and in hypertensives (Laurent *et al.*, 2001). On the other hand, it is known that inflammation plays a role in the development of atherosclerosis (Ross, 1999). High-sensitivity C-reactive protein (hCRP), the blood level of which can now be measured, has recently been examined as a possible marker of atherosclerosis development (Ridker *et al.*, 2000). Therefore, to clarify the relationships between adiponectin level and the development of atherosclerosis and insulin sensitivity, we have performed an epidemiological study to determine the role of adiponectin in the development of insulin resistance and atherosclerosis in inhabitants of rural communities in Japan.

Design and methods

Subjects

We have conducted an epidemiological study on cardiovascular diseases in two rural communities in Hokkaido, the northern island of Japan. A total of 383 male inhabitants, whose ages ranged from 18 to 90 years (average age 65 years), were selected randomly for the studies. Those who had fasting glucose levels of > 7·8 mmol/l, who were on medication for diabetes or who had coronary heart or cerebral vascular disease were excluded from the study. Informed consent was obtained from all participants in the study. All subjects were examined in the morning after fasting for at least 10 h. After 15 min of rest in the sitting position, blood pressure was measured with a sphygmomanometer. The average of three consecutive measurements was calculated. Body mass index (BMI) was calculated as weight in kilograms divided by the square of the height in metres. The clinical characteristics of the subjects studied are shown in Table 1.

Table 1 Clinical and metabolic characteristics of subjects studied (n = 383)

	Mean ± SD	Minimum	Maximum
Age (years)	65 ± 11	18	88
BMI (kg/m^2)	23·8 ± 3·4	16·1	32·8
SBP (mmHg)	134 ± 8	90	160
HOMA index	1·7 ± 1·3	0·21	9·8
TC (mmol/l)	4·86 ± 0·72	3·13	7·44
TG (mmol/l)	1·39 ± 1·00	0·34	10·78
HDL-cholesterol (mmol/l)	1·29 ± 0·41	0·59	3·67
PWV (cm/s)	1650 ± 375	882	3496
Adiponectin (μg/ml)	6·8 ± 3·8	0·8	31·1
CRP (mg/l)	0·93 ± 1·22	0·04	5·0

Laboratory examinations

Serum total cholesterol (TC), serum TG, serum HDL-cholesterol, fasting blood glucose level and serum insulin level were measured in all subjects. Blood glucose was measured by the glucose oxidase method, and serum insulin level was measured by a radioimmunoassay (RIA) using insulin RIA beads (Dinabot, Tokyo, Japan). Insulin resistance was estimated from fasting plasma insulin and glucose using the homeostasis model assessment (HOMA), a computer-based model of glucose/insulin interactions, and the estimation was validated by comparison with results obtained using the hyperinsulinaemic–euglycaemic clamp technique (Matthews *et al.*, 1985). Adiponectin and hCRP levels were measured using an enzyme-linked immunosorbent assay (ELISA) method (Otsuka Pharmaceuticals, Tokushima, Japan).

Pulse wave velocity (PWV)

Aortic stiffness was assessed in all subjects by measuring brachial–ankle PWV, using a volume plethysmographic instrument (PWV/ABI; Colin Co., Ltd., Komaki, Japan), which records PWV, blood pressure, electrocardiogram and heart sounds simultaneously (Suzuki *et al.*, 2001). Each subject was examined in the supine position, with electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on

the left edge of the sternum, and cuffs wrapped around both brachia and ankles. The pulse volume waveforms were recorded using a semiconductor pressure sensor. Data on volume waveforms for the brachium and ankle were stored, and the sampling time was 10 s with automatic gain analysis and quality adjustment. Subjects who showed an ankle–brachial pressure index (API) of less than 0·9 were excluded from the study.

Statistical analyses

The STATVIEW package (version 5·0) was used for statistical analysis. All numerical values were expressed as means ± standard deviations. Analyses were performed on the natural logarithm of HOMA, adiponectin, serum TG and hCRP to reduce the positive skew in the distribution. A P-value less than 0·05 was considered to be statistically significant.

Results

Insulin resistance and lipid profile

Table 1 shows the characteristics of the subjects. Table 2 shows correlations between log adiponectin and other variables. Significant negative correlations between log adiponectin and BMI ($r = -0·35$, $P < 0·001$) and between log adiponectin and log HOMA ($r = -0·50$, $P < 0·001$) were found in all subjects. Significant correlations were also found between log adiponectin and TC ($r = -0·10$, $P < 0·05$), log TG ($r = -0·36$, $P < 0·001$) and HDL-cholesterol ($r = 0·27$, $P < 0·001$). Age, log HOMA and log TG were independently correlated with log adiponectin and BMI, systolic blood pressure (SBP), TC and HDL-cholesterol were excluded by stepwise regression analysis for log adiponectin (Table 3). Multiple regression analysis for lipid profile was also performed; log adiponectin and log HOMA were found to be independently correlated with log TG and HDL but not with TC (Table 4).

Atherosclerosis

There was a significant positive correlation between log hCRP and log HOMA ($r = 0·15$, $P < 0·01$; Fig. 1). log hCRP also showed a significant positive correlation with age and a significant negative correlation with log adiponectin (data not shown). Multiple regression analyses for log hCRP revealed that log adiponectin and age were independently correlated with log hCRP. When log HOMA was added to this analysis, log HOMA was found to be independently correlated with log hCRP, but log adiponectin did not appear to be a significant predictor of log hCRP ($\beta = -0·24$, $P = 0·06$; Table 5). On the other hand, not only PWV but also log adiponectin showed strong positive correlations with age (Fig. 2), but there was no correlation between PWV and log adiponectin in all subjects (data not shown). As aging itself generally facilitates atherosclerosis of vessels, we

Table 2 Correlation between log adiponectin and other variables

Variable	r	P
Body mass index	−0·35	< 0·001
log HOMA	−0·50	< 0·001
Total-cholesterol	−0·10	< 0·05
HDL-cholesterol	0·27	< 0·001
log triglyceride	−0·36	< 0·001
Age	0·32	< 0·001
Mean blood pressure	−0·01	0·97

Table 3 Stepwise regression analyses for log adiponectin

Variable	β	SE	P
Age	0·26	0·01	< 0·0001
log HOMA	−0·43	0·036	< 0·0001
log TG	−0·15	0·046	< 0·01
BMI	−0·05	0·003	0·26
SBP	0·06	0·001	0·19
TC	−0·04	0·0001	0·40
HDL-cholesterol	0·01	0·001	0·13

Table 4 Multiple regression analyses for TC, TG and HDL-cholesterol

	Variable	β	SE	P
TC	log adiponectin	−8·9	7·6	0·24
	log HOMA	6·5	5·5	0·24
log TG	log adiponectin	−0·2	0·1	< 0·001
	log HOMA	0·2	0·04	< 0·001
HDL-cholesterol	log adiponectin	8·8	3·8	< 0·05
	log HOMA	−14·9	2·8	< 0·001

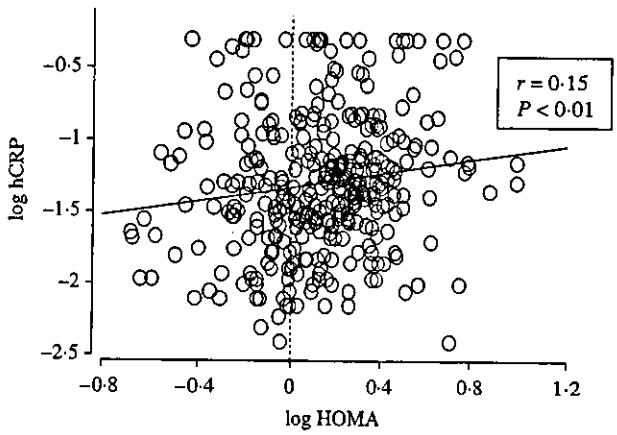

Fig. 1 Correlations between hCRP and HOMA.

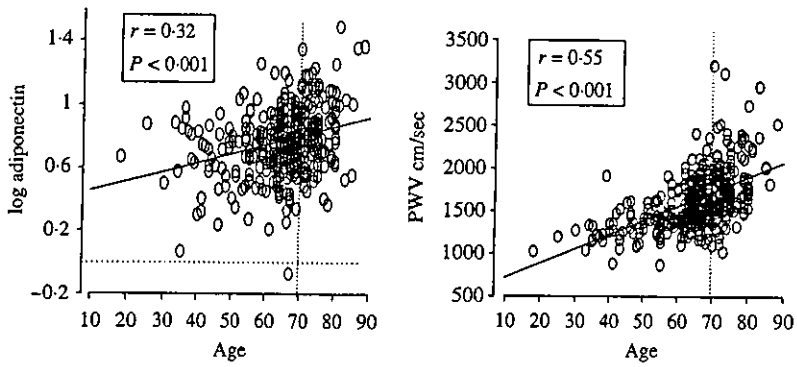

Fig. 2 Correlations between adiponectin, PWV and age.

Table 5 Multiple regression analyses for log hCRP

Variable	β	SE	*P*
log adiponectin	−0·38	0·11	< 0·01
Age	0·012	0·002	< 0·01
log adiponectin	−0·24	0·125	0·06
Age	0·012	0·002	< 0·01
log HOMA	0·22	0·086	< 0·05

Table 6 Multiple regression analyses for PWV in the group aged 70 years or less ($n = 254$)

Variable	β	SE	*P*
log adiponectin	−163·4	78·1	< 0·05
Age	14·7	1·64	< 0·01
log adiponectin	−103·0	86·7	0·21
Age	14·8	1·64	< 0·01
log HOMA	101·6	62·2	< 0·05

performed multiple regression analysis using data obtained only from subjects equal to or less than 70 years old. The results of multiple regression analysis indicated that log adiponectin and age were independently correlated with PWV. When log HOMA was added to this analysis, log HOMA was found to be independently correlated with PWV, but log adiponectin level did not appear to be correlated with PWV significantly ($\beta = -103{\cdot}0$, $P = 0{\cdot}21$; Table 6).

Discussion

Adiponectin is an adipocyte-secreted protein of 247 amino acids that exists abundantly in plasma at concentrations ranging from 5 to 30 mg/l (Arita *et al.*, 1999). Several recent studies have suggested that adiponectin plays a role in modulation of glucose metabolism and insulin sensitivity (Hotta *et al.*, 2000; Berg *et al.*, 2001). In the present study, we found that adiponectin level was correlated negatively with BMI or HOMA, and the results of stepwise regression analysis showed that age and HOMA were independently correlated with adiponectin level. Consistent with the results of the above-mentioned previous studies, adiponectin level was found to be strongly related to insulin resistance without influence of obesity. Recent studies have demonstrated that administration of adiponectin to rodents increases insulin-induced tyrosine phosphorylation of the insulin receptor in skeletal muscle. Yamauchi *et al.* (2001) reported that adiponectin-treated KKAy mice showed increased expression of enzymes involved in β-oxidation and uncoupling protein (UCP) 2 in skeletal muscle. In addition, in mice treated with adiponectin, acyl coenzyme A oxidase (ACO) activities and free fatty acid (FFA) combustion were increased in skeletal muscle, leading to a decrease in tissue triglyceride content, in association with decreased serum FFA and TG levels. Increased tissue TG content has been reported to interfere with insulin-stimulated activation of phosphatidylinositol-3-kinase and subsequent translocation of glucose-transporter protein 4 (GLUT4) and uptake of glucose, leading to insulin resistance (Shulman, 2000). Thus, a decrease in TG content in skeletal muscle might contribute to improvement in insulin signal transduction. We previously reported (Furuhashi *et al.*, 2002) that fructose-fed rats, an insulin-resistant hypertensive model, showed increased intramuscular triglyceride levels compared with those in control rats and that TG level in the muscle of fructose-fed rats was negatively correlated with insulin sensitivity. The results of multiple regression analysis for lipid profile carried out in the present study showed that adiponectin level and HOMA were independently correlated with TG and HDL-cholesterol but not with TC. This means that adiponectin level is not only correlated with insulin sensitivity but also directly affects lipid metabolism. Hotta *et al.* (2000) reported that a significant negative correlation between adiponectin and serum TG levels and a positive correlation between adiponectin and serum HDL levels were found in patients with type 2 diabetes mellitus. The results of the present study extend this finding to nondiabetic male subjects and suggest that adiponectin plays an important role in regulation of lipid

metabolism, which in part is independent of improvement in insulin sensitivity.

On the other hand, hypoadiponectinaemia is associated strongly with the incidence of CAD. Hotta *et al.* (2000) analysed the plasma adiponectin concentrations in age- and-BMI matched nondiabetic and type 2 diabetic subjects with and without CAD. The plasma adiponectin concentrations in diabetic patients with CAD were found to be lower than those in diabetic patients without CAD, and they suggested that the decreased plasma adiponectin concentrations in diabetes patients might be an indicator of macroangiopathy. Ouchi *et al.* (2003) reported that adipose tissue expresses CRP and found a reciprocal association between CRP and adiponectin in blood and adipose tissue. It is well known that plasma hCRP levels are positively associated with total body fat mass, and that body weight loss reduces plasma hCRP levels. In the present study, we also found that adiponectin level was negatively correlated with BMI and positively correlated with age. There was no correlation between age and BMI in our study. Although the reason why adiponectin positively correlates with age is unclear; it has been reported that adiponectin is negatively regulated by androgen (Nishizawa *et al.*, 2002), and it is therefore possible that androgen level decreases and adiponectin level increases with aging. Adiponectin level was also negatively correlated with hCRP as a possible marker of atherosclerosis. Multiple regression analyses for hCRP revealed that adiponectin level was independently correlated with hCRP after adjustment with BMI, but adiponectin level did not appear to be a significantly correlated with hCRP when HOMA was added to this analysis. On the other hand, because PWV is strongly correlated with age, we tried excluding older people who are thought more likely to have atherosclerosis. Multiple regression analysis revealed that adiponectin level was independently correlated with PWV in subjects less than 70 years old. In order to evaluate different age groups, we also divided subjects into three groups – less than 65 years, from 65 to 70 years and over 70 years – and evaluated correlation between adiponectin and PWV. The results for the groups less than 65 years and from 65 to 70 years were no different from subjects aged 70 years or less, so the age of 70 as the dividing point to evaluate the correlation between adiponectin and PWV is adequate in the community. However, adiponectin also appeared not to correlate significantly with PWV when HOMA was added to this analysis; HOMA was still independently correlated with hCRP and PWV. These results are compatible with adiponectin having an antiatherogenic effect and modulating insulin sensitivity (Okamoto *et al.*, 2003). To the best of our knowledge, this is the first report of adiponectin level being negatively correlated with atherosclerosis indexes such as hCRP or PWV in nondiabetic subjects. In tissue-cultured cell experiments, adiponectin suppressed tumour necrosis factor-α (TNF-α)-induced mRNA expressions of several adhesion molecules, including vascular cell adhesion molecule-1, intracellular adhesion molecule-1 and E-selectin, in vascular endothelial cells and suppressed monocyte attachment to endothelial cells (Ouchi *et al.*, 2000). Kubota *et al.* (2002) generated adiponectin-deficient mice and carried out experiments to determine whether adiponectin has direct protective effects on atherosclerosis *in vivo*. These studies suggested that adiponectin has both anti-inflammatory and anti-atherosclerotic effects. Taking these findings into consideration, hypoadiponectinaemia may be involved in the pathophysiology of atherosclerosis both directly and through aggravation in insulin resistance.

In contrast with many other adipocyte-derived hormones, such as leptin, TNF-α, FFA and plasminogen activator inhibitor 1, plasma adiponectin levels were found to be reduced in obese animals and humans. However, the mechanism by which adiponectin production is regulated has not been elucidated. β-Adrenergic agonists (Fasshauer *et al.*, 2001), TNF-α (Kappes & Loffler, 2000) and glucocorticoids (Fasshauer *et al.*, 2002) have been reported to inhibit gene expression and secretion of adiponectin. As mentioned earlier, Nishizawa *et al.* (2002) reported that plasma concentrations of adiponectin are lower in men than in women and that androgens decrease plasma adiponectin levels. It is well known that androgen levels decrease with aging in males. This might be one of the mechanisms by which adiponectin is positively correlated with age in male subjects, as was found in the present study.

This study was undertaken to determine the validity of the hypothesis that adiponectin is involved in lipid metabolism and atherosclerosis, independent of insulin resistance. Our results provide evidence that hypoadiponectinaemia might be one of the independent risk factors for atherosclerosis. Our results also suggest that adiponectin is one of the underlying factors in the metabolic syndrome, a concurrence of disturbed metabolism, overweight and abdominal fat distribution, mild dyslipidaemia and hypertension, which plays a key role connecting insulin resistance and lipid disorder with atherosclerosis. Further studies are needed to clarify this possibility.

In summary, adiponectin may correlate with atherosclerosis either directly or indirectly through improvement of insulin resistance. Although its regulatory mechanism has not been clarified, further examination of this new 'adipocytokine' may provide further insights into the relationship between atherosclerosis and insulin resistance.

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研究成果の刊行に関する一覧表

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ERROR MANAGEMENT

Adverse drug events and medication errors: detection and classification methods

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Investigating the incidence, type, and preventability of adverse drug events (ADEs) and medication errors is crucial to improving the quality of health care delivery. ADEs, potential ADEs, and medication errors can be collected by extraction from practice data, solicitation of incidents from health professionals, and patient surveys. Practice data include charts, laboratory, prescription data, and administrative databases, and can be reviewed manually or screened by computer systems to identify signals. Research nurses, pharmacists, or research assistants review these signals, and those that are likely to represent an ADE or medication error are presented to reviewers who independently categorize them into ADEs, potential ADEs, medication errors, or exclusions. These incidents are also classified according to preventability, ameliorability, disability, severity, stage, and responsible person. These classifications, as well as the initial selection of incidents, have been evaluated for agreement between reviewers and the level of agreement found ranged from satisfactory to excellent (κ = 0.32–0.98). The method of ADE and medication error detection and classification described is feasible and has good reliability. It can be used in various clinical settings to measure and improve medication safety.

Medications are the most frequent cause of adverse events, and such injuries are called adverse drug events (ADEs).[1 2] ADEs are common in most clinical settings including adult inpatients with a reported incidence of 6.5%,[3] adult outpatients with an incidence of 27.4%,[4] and pediatric inpatients with a reported incidence of 2.3%.[5] These ADEs have substantial consequences including hospital admissions, prolonged hospital stay, additional resource utilization, and time away from work, as well as lower patient satisfaction.[6 7]

Some ADEs are caused by errors called medication errors.[2] Medication errors are much more frequent than ADEs but only a small minority actually cause ADEs.[2] In one inpatient study the frequency of medication errors was 5.3 per 100 medication orders, much higher than the ADE rate of 0.25 per 100 orders.[2] Another recent report from 36 hospitals which evaluated the administration stage in particular showed that 19% of medication administrations contained an error.[8]

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The goal of research in ADEs and medication errors is to reduce the likelihood of harm related to medications. To do this it is essential to be able to describe the epidemiology of these problems. Building on previous work, we have developed over the last decade a methodology for identifying and classifying medication safety issues which we present here so that others may use these methods to investigate ADEs and medication errors in their own settings. We also describe the strengths and limitations of this approach, including assessment of reliability.[9]

The methodology includes:

- definitions of incidents (ADEs, medication errors, and other drug related terms);
- general processes for identifying them;
- case identification methods (practice data review, self-reports from health professionals, and patient surveys);
- comparison of methods;
- methods for classifying incidents; and
- tools for validating the findings.

METHODOLOGICAL APPROACH

Definition of incidents

An incident includes any irregularity in the process of medication use. It might represent an ADE, potential ADE, medication error, or none of these—it is essentially a "catch all" term for what to call something before it has been classified. An incident can occur at any point in the medication use process (ordering, transcribing, dispensing, administrating, and monitoring). There are several ways to categorize incidents: actual (ADEs) *v* potential; preventable *v* non-preventable; ameliorable *v* non-ameliorable; and error *v* non-error. These categories may overlap and it is important to understand their relationship with each other (fig 1).

A medication error can occur at any step of the medication use process. Some ADEs are associated with medication errors and all potential ADEs are medication errors (fig 1). Minor errors that have little or no potential for harm are not considered potential ADEs—for example, a dose of non-critical medication such as docusate is given several hours late—but are considered to be medication errors. If the incident has the potential to harm a patient—for example, a dose of critical medication such as an intravenous antibiotic is not given—it is considered both a medication error and a potential ADE.

A potential ADE is a medication error with the potential to cause an injury but which does not

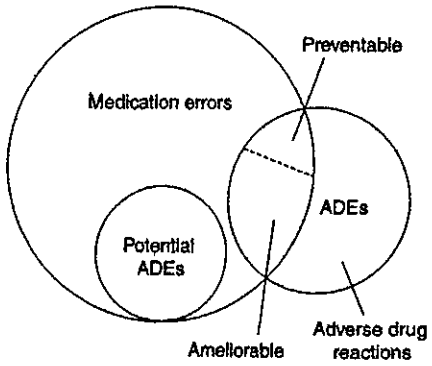

Figure 1 Relationship between adverse drug events (ADEs), potential ADEs, and medication errors.

actually cause any injury, either because of specific circumstances, chance, or because the error is intercepted and corrected—for example, an order is written for an overdose of medication but the error is intercepted by the pharmacist.

An ADE is an injury due to a medication—for example, cough due to angiotensin converting enzyme (ACE) inhibitors is considered an ADE. ADEs may or may not result from medication errors—for example, cough due to an ACE inhibitor in a patient without a history of ACE inhibitor induced cough is not the result of a medication error, while a medication error has occurred if the patient has a prior history of ACE inhibitor induced cough.

A preventable ADE is an injury that is the result of an error at any stage in the medication use—for example, a coma due to an overdose of a sedative. A non-preventable ADE is an injury due to a medication where there is no error in the medication process—for example, an allergic reaction in a patient not previously known to be allergic to the medication. These are also known as adverse drug reactions, or non-preventable reactions due to side effects or allergic reactions. An ameliorable ADE is an injury of which the severity or duration could have been substantially reduced if different actions had been taken—for example, sexual dysfunction lasting for several months while taking a selective serotonin reuptake inhibitor. A non-ameliorable ADE is an injury in which there is no current reasonable way to reduce the severity or duration—for example, bradycardia after the first usual dose of β blocker.

General process for identifying incidents

Our group has used three methods to collect incidents: (1) collecting practice data, (2) soliciting any incidents from health professionals, and (3) surveying patients for drug related events (fig 2). Other methods such as direct observation have also been used and this approach in particular is highly effective for detecting administration errors.[8] Practice data sources include charts, laboratory, and prescription data, as well as administrative data.

In the inpatient setting, the Institute for Healthcare Improvement has suggested that the following sections require particular attention: discharge summary (may include ADEs), procedure notes (narrative sections for ADEs), physician progress notes (changes in plan of care related to effects of medications), laboratory reports (pertinent laboratory results), physician orders (pertinent medications), and nursing/multidisciplinary progress notes (symptoms related to ADEs).[10] These data sources may be used individually or in combination to identify possible incidents. Trained research pharmacists, nurses, assistants, or physicians as well as pharmacy externs and medical students can usually do the review of charts, laboratory, and prescription data manually. This review can also be automated using rule sets to extract data from electronic medical records (EMR) or computerized physician order entry (CPOE) in order to target possible incidents more efficiently.[11]

Screening of administrative data is usually based on ICD-9 coding associated with ADEs and medication errors such as poisoning or urticaria, although it can also include drug and laboratory data if available. This screening is usually computerized. The Agency for Healthcare Research and Quality (AHRQ) has developed patient safety indicators which are based on administrative data and use ICD-9 coding.[12] All patient safety indicators are associated with injuries from medical care, but not always with ADEs and medication errors. For example, the indicators include iatrogenic pneumothorax which is not related to ADEs or medication errors. On the other hand, complications of anesthesia include an overdose of anesthetic medications which is a medication error. Because the indicators and the calculation programs on the commercial statistical packages for administrative data are publicly provided, they can be used as a tool for screening. Overall, however, the positive predictive value of ICD-9 codes for ADEs is very low (about 2%) and is much lower for medication errors.[13]

Regardless of the method of identification, incidents are then generally presented to two independent reviewers who independently categorize them into ADEs, potential ADEs, medication errors, or exclusions. At the same time the reviewers classify the incidents according to a variety of parameters such as preventability and severity.

Case identification

Data review

In reviewing charts, laboratories, and prescription data, the reviewing process will differ somewhat between facilities with an EMR or CPOE system and those without them. At sites without an EMR or CPOE system the research nurses, pharmacists, or research assistants review charts, laboratory results, and prescriptions and identify any possible incident during the study period. Prescription data can be collected by screening carbon copies of prescriptions.

With an EMR or CPOE system reviewers can also review all the documents and data on the computer, but automatic extraction using computer programs and text searching or natural language processing can detect any keywords such as "allergy" or "falls", specific laboratory values such as potassium levels of 6.5 mEq/l, or drug names such as an angiotensin II receptor blocker.[11] These concepts can be linked to form rules—for example, heparin and low hematocrit. A positive yield from a rule is called a trigger. The use of triggers is much more practical and less labor intensive than conventional chart reviewing because the triggers can be automated by computer and the reviewer's search is much more focused. Gurwitz and colleagues[14] used computer based triggers and other means to find 1523 ADEs from 27 617 patients; the computer based triggers found 66% of ADEs. Triggers can also be used to monitor for ADEs and medication errors in daily practice once their discrimination ability is established.[15] Specific drugs, combinations of drugs, symptoms, ICD-9 related diagnoses, and laboratory results can all be used as triggers. These triggers from an EMR or CPOE are then reviewed by the research nurses, pharmacists, or research assistants and assessed as incidents or not. Written text or other information in the chart can be used in this evaluation. Honigman and colleagues[16] transformed EMR data such as physician progress notes or laboratory results to text data and cleaned them for spelling, syntax, abbreviation, and inconsistency. The text data were then screened for possible incidents using a computer program.

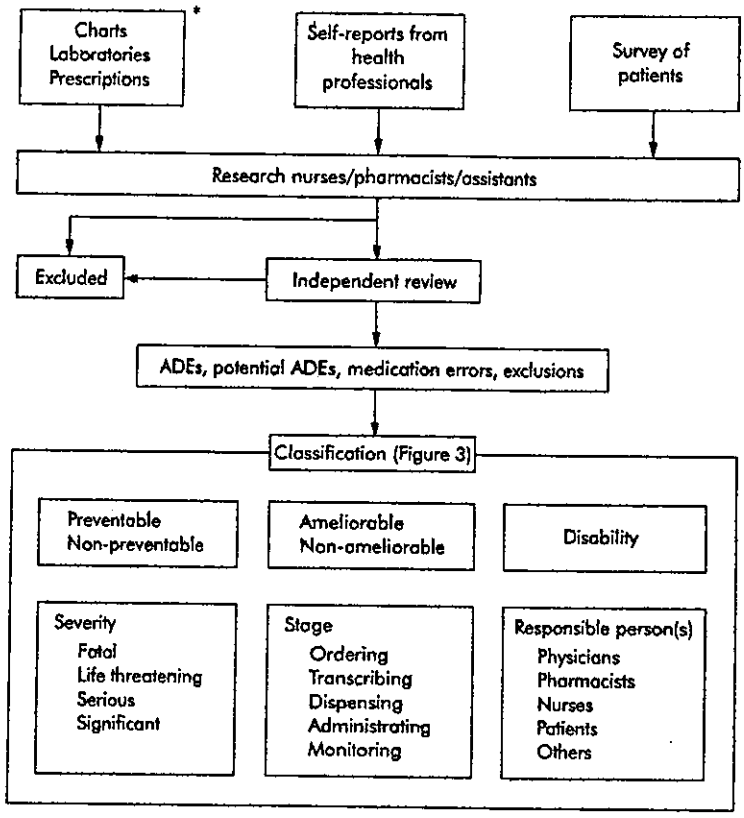

Figure 2 General process for finding adverse drug events (ADEs), potential ADEs, and medication errors. *Computerized or not.

When reviewing practice data the general rule to determine if an incident is related to a medication is to look for any irregularity in the patient's condition such as change in mental status, sudden drop in blood pressure, sudden drop in oxygen saturation, new rash, or new diarrhea, and then to consider whether it might be related to a medication (table 1). If a likely relationship is present and these symptoms cannot be accounted for by underlying diseases or other plausible reasons, they are considered incidents. Certain actions among health professionals can be clues in identifying the incidents—for example, changes or clarification to a physician's order, time changes on the medication administration record, outdated narcotic orders, late administration of drugs, order for *Clostridium difficile* toxin test or culture, and new allergy listed in the medication record (table 1). Many specific diagnoses associated with ADEs and medication errors can also be reviewed to identify incidents. The diagnoses are usually defined by ICD-9 codes, and extraction of the ICD-9 codes is usually done from administrative data (table 2).

Medication prescribing can also be evaluated to identify incidents. Prescribing certain drugs implies the occurrence of an incident (table 3)—for example, when diphenhydramine is given it is often to treat a reaction to another medication. Combinations of drugs should also be evaluated for incidents including drug–drug interactions that are frequently observed in practice (table 4).

Combinations of drugs and other factors also provide important clues for incidents (tables 5 and 6). The symptoms or diagnoses may or may not have a previously demonstrated association with the listed drugs. If plausible reasons other than medication use appear to have caused symptoms or diagnoses, they would be considered as events independent of drugs and are excluded. Otherwise, they are considered incidents. Some combinations of drugs and miscellaneous factors are also considered (table 7). For example, women of childbearing age, elderly persons, patients on dialysis, and pregnant women should not take certain specific drugs. Acetaminophen (paracematol) is a frequently prescribed analgesic both alone and in combination with other

Table 1 Symptoms or actions suggesting an ADE, potential ADE, or medication error

Symptoms	Criteria
Change in mental status Sudden drop in blood pressure Sudden drop in oxygen saturation New rash New diarrhea	When causal drugs were administered in proximity suggesting drug was cause
Actions	**Criteria**
Changed or clarified physician's order	All
Time changes on the medication administration record	
Outdated narcotic orders	
Late doses	
Regular doses	Dose delayed >6 hours from order to administration
Stat doses	Dose delayed >1 hour from order to administration
Ordering *C difficile* toxin or culture	All
New allergy listed	

Table 2 Diagnoses associated with ADEs, potential ADEs, or medication errors

Diagnoses	ICD-9 code
Polyneuropathy due to drugs	357.6
Other specified gastritis	535.4
Nephritis and nephropathy	583.9
Contact dermatitis due to drug	692.3
Dermatitis due to drug	693.0
Urticaria	708
Late effect of poisoning due to drug	909.0
Poisoning by	
Antibiotics	960
Other anti-infective agents	961
Hormones and synthetic substitutes	962
Systemic agents	963
Agents that affect blood	964
Analgesics and antipyretics	965
Anticonvulsants/antiparkinsonian drugs	966
Sedatives and hypnotics	967
Other central nervous system depressants	968
Psychotropic agents	969
Central nervous system stimulants	970
Drugs primarily affecting autonomic nervous system	971
Cardiovascular drugs	972
Gastrointestinal tract drugs	973
Water, mineral, and uric acid metabolism drugs	974
Agents acting on muscles and respiratory tract	975
Topical agents	976
Other and unspecified drugs	977
Anaphylactic shock, not elsewhere classified	995.0
Adverse effect of drug, not elsewhere specified	995.2

analgesics. Because patients can receive multiple forms of this agent resulting in an excessive daily dose, the cumulative dose should be assessed for possible excessive dosing. Patients who ingest non-steroidal anti-inflammatory drugs (NSAIDs) or selective cyclooxygenase (COX II) inhibitors may develop gastrointestinal problems, and those patients who undergo oesophagogastroduodenoscopy often have these problems because of these drugs.

Laboratory triggers are useful for detecting incidents, especially when the review process is assisted by computerized rules.[11] Some abnormal laboratory values themselves, even when there are no symptoms, are considered possible incidents because of the likelihood they have been caused by a medication. In the reviewing process all cases of hepatotoxicity (raised transaminase or bilirubin) and renal dysfunction (raised creatinine or BUN) that cannot be associated with another clinical issue and are associated with medication use are generally considered as incidents. In addition, some specific abnormal laboratories or inappropriate monitoring of medications are incorporated into the computerized rules to detect incidents (table 8).

Reports

There are two main types of self-report from health professionals: those from physicians, nurses, pharmacists, or other health professionals who become aware of any ADE, potential ADE, or medication error (sometimes called an "incident report"), and those generated by research assistants, nurses, or patient safety officers who visit wards or clinics to solicit any possible incident and record it.[3] The process of using self-reports from health professionals is especially useful for identification of incidents in inpatient settings.[3] Investigation of iatrogenic disorders such as ADEs and medication errors always provokes concerns about liability among health professionals and such concerns may inhibit the self-report.[17] It is thus important to educate health professionals about the purpose of the study, which is to clarify the treatable factors associated with ADEs and

Table 3 Use of specific drugs suggesting that an ADE may have occurred

Drugs	Possible ADE
Angiotensin II receptor blocker	Angiotensin converting enzyme inhibitor allergy
Diphenhydramine	General drug allergy
Flumazenil	Excessive benzodiazepine dose
Sodium Polystyrene Sulfonate	Drug induced hyperkalemia
Naloxone	Excessive narcotic dose
Nystatin or clotrimazole troche	Drug induced fungal infection
Oral metronidazole or vancomycin	Drug induced *Clostridium difficile*
Phytonadione	Excessive coagulation therapy
Topical steroids	Cutaneous drug allergy
Vaginal antifungal agents	Drug induced fungal infection

medication errors and not to reprimand the responsible individuals. A non-punitive culture is important to maximize data capture at the study sites.

Patient surveys

Because incidents may not be recorded in a patient's medical record, particularly in the outpatient setting, survey methods to elicit these types of incidents from patients

Table 4 Drug combinations

First drug	Second drugs
Drug–drug interactions	
Allopurinol	Mercaptopurine
Alprazolam	Fluconazole, itraconazole, ketoconazole (oral), miconazole (oral)
Carbamazepine	Azithromycin, clarithromycin, clozapine, dirithromycin, erythromycin, isoniazid, propoxyphene, verapamil
Cimetidine	Phenytoin, propranolol, warfarin
Cyclosporine	Azithromycin, clarithromycin, dirithromycin, erythromycin
Dextroamphetamine	Selegiline
Digoxin	Azithromycin, clarithromycin, dirithromycin, erythromycin
Fluconazole	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin
Gemfibrozil	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin
Hydrochlorothiazide	Colchicine
Ketoconazole (oral)	Atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, simvastatin
Lithium carbonate	Acetazolamide, hydrochlorothiazide
Meperidine	Phenelzine
Methotrexate	Aspirin, choline magnesium trisalicylate, methocarbamol
Sildenafil	Erythrityl tetranitrate, isosorbide, nitroglycerin
Tacrolimus	Azithromycin, clarithromycin, dirithromycin, erythromycin
Theophylline	Ciprofloxacin, gatifloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin, ofloxacin, sparfloxacin
Triazolam	Fluconazole, itraconazole, ketoconazole (oral), miconazole (oral)
Warfarin	Levothyroxine, liothyronine
Duplicate drugs	
ACE inhibitors	ACE inhibitors
Beta blockers	Beta blockers
Calcium channel blockers	Calcium channel blockers
HMG CoA reductase inhibitors	HMG CoA reductase inhibitors
NSAIDs	COX II inhibitors
Sulfonylureas	Sulfonylureas

ACE, angiotensin converting inhibitor; NSAID, non-steroidal anti-inflammatory drug.